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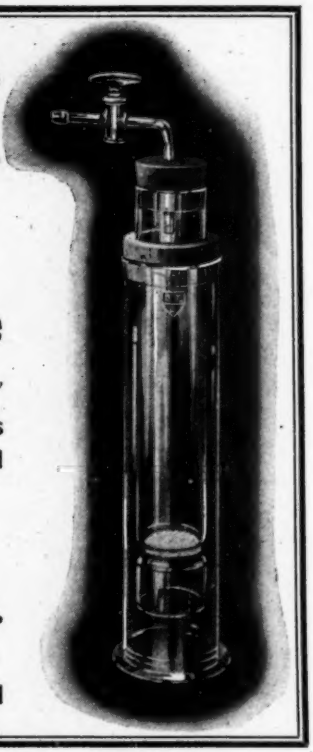

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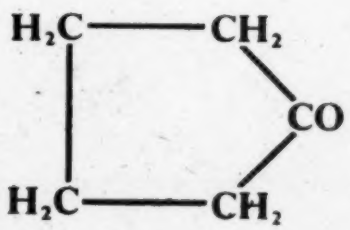

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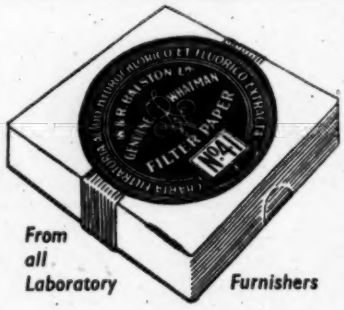

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percentages of individual alkaloids were isolated: *l*-hyoscyamine, 1·97; *l*-hyoscine, 0·06; *dl*-hyoscine, 0·05; norhyoscyamine, 0·01; and a new alkaloid, 0·06, all expressed on the drug.

The drug showed no well-defined macroscopic differences from the *Duboisia* previously examined by Barger, Martin, and Mitchell, but only the dried leaves were available for examination: a comparison of the flowering specimens would probably have shown some characteristic differences. Dr. Metcalfe, of the Royal Botanic Gardens, Kew, very kindly undertook the botanical examination of the drugs. In the absence of flowering material this was rendered more difficult, but as a result of consideration of the stomatal distribution on the upper and the lower leaf surfaces it was possible to state with a fair degree of certainty that the material formerly found to contain no hyoscyamine was in fact authentic *D. myoporoides*, whereas the present specimen was probably *D. Leichhardtii*. Whatever the exact botanical distinction, the important point would appear to be that these two distinct types of *Duboisia*, and possibly other intermediate forms, have appeared on the market simply as "Duboisia" or "Duboisia myoporoides." This fact, which appears to be supported by recent work on *Duboisia* referred to in the Sixteenth Annual Report of the Council for Scientific and Industrial Research, Australia, for the year ended 30th June, 1942, would account for the discrepancies between the results of various investigators, and has almost certainly led to confusion in the past.

The new alkaloid, $C_{13}H_{23}O_2N$, referred to above was similar to tigloidine, valeroidine, and the poroidines in that its *hydrobromide* was very soluble in chloroform. It was optically inactive and saturated. On hydrolysis it yielded tropine and a liquid acid thought to be a valeric acid. It was not possible to identify this latter with certainty, but it is probably mainly *iso*valeric acid. iso*Valeryltropëine hydrobromide* was synthesised but was not identical with the above hydrobromide. It is quite possible, as in the case of "Base Z," which was later shown to consist of a mixture of the isomers, poroidine and *iso*poroidine (*ibid.*), that this material is also an isomeric mixture, but owing to the very small amount of material available it was not possible to pursue the matter further. Since its constitution is thus not definitely established it is suggested that the material be identified by the name "*Base D*". It is of interest to note that whereas *D. myoporoides* yielded minor alkaloids which were esters of ψ-tropine, a dihydroxytropane, and nortropine respectively, *D. Leichhardtii* has yielded a minor alkaloid which is an ester of tropine, and that except in the case of tigloidine, which was tiglyl-ψ-tropëine, they were all pentoic acid esters.

Experimental.

Isolation and Separation of the Alkaloids.—The drug (No. 20 powder) was extracted with cold alcohol, and the total alkaloids isolated by the usual methods. They were converted into hydrobromides, and the solution concentrated, but no crystalline material could be isolated. The hydrobromides were then converted into neutral oxalates, and the solution concentrated. Partly racemised hyoscyamine oxalate (29 g.), m. p. 190° (corr.), was separated. The mother-liquor would not yield any further crystalline material, and small amounts were therefore converted severally into hydrobromide, sulphate, neutral phosphate, borate, picrate, and *d*-camphorsulphonate. None of these solutions crystallised after concentration.

The various solutions were united, basified with ammonia, and the alkaloids extracted with chloroform. The chloroformic solution was fractionally extracted with aqueous N-oxalic acid, and the various fractions concentrated. These all crystallised, and yielded a total of 19·5 g. of partly racemised hyoscyamine oxalate, m. p. ranging from 188° to 194° (corr.). By repeated refractionation of the mother-liquors from this material, a further quantity of 13·5 g. was obtained, making a total of 62 g., equivalent to 1·97% of hyoscyamine alkaloid on the drug. In addition, 0·35 g. of an oxalate, m. p. 227—228° (corr.), was separated; this was norhyoscyamine oxalate (see below).

The final mother-liquors from the oxalates were united, basified with ammonia, and the alkaloids extracted with chloroform and converted into hydrobromides. The concentrated solution was extracted with two portions of chloroform (15; 15 ml.). The residue from the chloroform slowly crystallised, and the crystals were collected and washed with acetone; this was "*Base D*" *hydrobromide* (see below).

The aqueous solution of the hydrobromides so extracted was concentrated and chilled. Crystals (2·3 g.), m. p. 184° (corr.), separated. Further concentration of the mother-liquor yielded a second crop (1·9 g.), m. p. 167° (corr.); these were respectively the hydrobromides of *l*-hyoscine and *dl*-hyoscine (see below).

Purification of the Separate Alkaloids.—Hyoscyamine. The various fractions of partly racemised hyoscyamine oxalate were dissolved in water, basified with ammonia, and the alkaloid extracted with chloroform. After racemisation by the addition of a small amount of sodium hydroxide to its cold alcoholic solution (Will, *Ber.*, 1888, **21**, 1723), the alkaloid was converted into hydrobromide. The resultant material crystallised from alcohol–acetone in opaque white nodules, m. p. 163·5° (corr.) not depressed by authentic atropine hydrobromide (Found: C, 55·3; H, 6·2; N, 3·9; Br, 21·0. Calc. for $C_{17}H_{23}O_3N,HBr$: C, 55·1; H, 6·5; N, 3·8; Br, 21·6%).

Norhyoscyamine. The oxalate, m. p. 227—228° (0·35 g.), was repeatedly recrystallised from acetone containing a trace of water and thereby obtained in felted needles, m. p. 249° (corr.) [Found: C, 63·2; H, 6·5; N, 4·6. Calc. for $(C_{16}H_{21}O_3N)_2,H_2C_2O_4$: C, 63·7; H, 6·9; N, 4·4%]. No authentic material was available for comparison.

Hyoscine. Each of the two crops of hydrobromide obtained was recrystallised first from alcohol–ether and then from water; in each case colourless, efflorescent prisms were thereby obtained: From first crop, m. p. 195—196° (corr.) not depressed by authentic *l*-hyoscine hydrobromide (Found: C, 46·9; H, 6·3; N, 3·2; Br, 18·3. Calc. for $C_{17}H_{21}O_4N,HBr,3H_2O$: C, 46·6; H, 6·4; N, 3·2; Br, 18·3%); $[\alpha]_D^{20°}$ −24·4° (*c*, 5·0 of anhydrous salt in water). From second crop, m. p. 185° (corr.) not depressed by authentic *dl*-hyoscine hydrobromide (Found: N, 3·2; Br, 18·4. Calc. for $C_{17}H_{21}O_4N,HBr,3H_2O$: N, 3·2; Br, 18·3%); it was optically inactive (*c*, 5·0 of anhydrous salt in water).

"*Base D.*" The *hydrobromide* crystallised from dry acetone in glistening plates, m. p. 231° (corr.) depressed to *ca.* 205° by tigloidine hydrobromide (m. p. 234—235°) with which it was at first thought to be identical (Found: C, 50·6; H, 7·6; N, 4·6; Br, 26·0. $C_{13}H_{23}O_2N,HBr$ requires C, 51·0; H, 7·8; N, 4·6; Br, 26·1%); it was optically inactive (*c*, 8·0 in water), and very soluble in chloroform, water, and alcohol.

Hydrolysis of "Base D."—The base from 0·4 g. of hydrobromide was boiled for 2 hours with barium hydroxide (0·75 g.) in water (10 ml.). After removal of the barium as sulphate, the acid filtrate was extracted with ether, which left 0·09 g. of an oily acid with a powerful odour of valeric acid; yield, 68%. The *p*-phenylphenacyl ester, m. p. 78° (corr.), formed dull, colourless laminæ from 60% alcohol. The m. p. was depressed to *ca.* 68° by mixing with an equal weight of

the ester (m. p. 76°) of *iso*valeric acid and differs from those of the other three isomeric esters; the material is possibly a mixture of two of these. *p*-Phenylphenacyl tiglate was made for comparison and formed glistening laminæ, m. p. 104—105° (corr.).

The solution from which the valeric acid had been extracted was neutralised with sodium hydroxide and concentrated (5 ml.). It was basified with an equal volume of 50% aqueous sodium hydroxide solution and repeatedly extracted with chloroform. The residue from the chloroform was boiled for 1 hour with acetic anhydride (5 ml.), and the product isolated and purified in the usual manner. Colourless, prismatic needles were thus obtained (from alcohol–ether), m. p. 188° (corr.) not depressed by authentic acetyltropëine hydrobromide, but depressed to 145° by acetyl-ψ-tropëine hydrobromide (m. p. 205°).

Synthesis of iso*Valeryltropëine Hydrobromide.*—Tropine (2·8 g.) was titrated with hydrochloric acid and the solution evaporated in a vacuum. Tropine hydrochloride so obtained was esterified with *iso*valeryl chloride (3 g.), and the product isolated and purified as in the case of tigloidine (*loc. cit.*). It formed colourless, pearly plates from alcohol–ether, and was extremely soluble in water, chloroform, and alcohol, but insoluble in ether, and was deliquescent (Found: C, 51·1; H, 7·7; N, 4·6; Br, 25·9. $C_{13}H_{23}O_2N,HBr$ requires C, 51·0; H, 7·8; N, 4·6; Br, 26·1%); m. p. 225—227° (corr.) depressed to *ca.* 200° by "Base D" hydrobromide; yield 60%.

My thanks are due to Messrs. T. and H. Smith, Ltd., Edinburgh, for supplies of material, to Wm. F. Martin, Esq., F.R.I.C., for his continued interest and advice, and to The Royal Botanic Gardens, Kew, for the botanical examination of the drugs.

Laboratories of Messrs. T. & H. Smith, Ltd., Edinburgh. [*Received, May 17th*, 1944.]

NOTE.

The Preparation of m-*Nitrobenzenesulphonyl Chloride.* By Herbert H. Hodgson and John S. Whitehurst.

The directions for making this compound from nitrobenzene and chlorosulphonic acid given in D.R.-P. 89,997 (cf. Friedländer, 1894—1897, IV, pp. 38—39) are insufficient for obtaining consistent results on a laboratory scale, and the following more detailed description has been found satisfactory: Dry nitrobenzene (123 g., 1 g.-mol.) and chlorosulphonic acid (350 g., 3 g.-mols.) are stirred together at room temperature until thoroughly mixed (any temperature rise indicates water in the nitrobenzene), the temperature is then raised gradually to 100°, maintained there for 2 hours, and thereafter kept at 110—120° for 6 hours. The initial yellow colour has now changed to brown and the reaction is completed by a final heating at 125—130° for 2 hours, *i.e.*, a total heating period of 10 hours. After cooling, the solution is poured into a mixture of ice (1 kg.) and water (1 kg.), and the white precipitate collected, washed with water, and air-dried. Yield, 170 g. (76% of the theoretical); m. p. 54°. The crude *m*-nitrobenzenesulphonyl chloride is purified by dissolution in glacial acetic acid (500 c.c.), the filtered solution cooled below 15° (otherwise dilution with water precipitates the compound as a semi-fused mass), and water (200 c.c.) added cautiously with stirring; *m*-nitrobenzenesulphonyl chloride then separates in colourless prismatic needles, which are washed with 50% acetic acid and air-dried; m. p. 62° (Armstrong, Colgate, and Rodd, *Proc. Roy. Soc.*, 1914, [*A*], **90**, 111, give m. p. 61·5—62°). Yield of purified product, 124 g. (55%).

The authors are indebted to the Charles Brotherton Trust for a Research Scholarship to one of them (J. S. W.), and to I.C.I. Ltd. (Dyestuffs Division), for gifts of chemicals.—Technical College, Huddersfield. [*Received, June 9th*, 1944.]

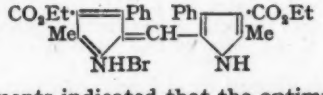
131. *Pyrrole Trimethincyanines.*

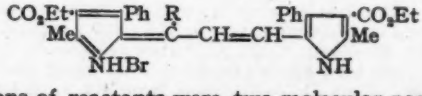
By A. H. Cook and J. R. Majer.

Pyrroles containing at least one α-free position have been found to condense with ketones and orthoformic ester in presence of mineral acid. The intensely coloured products have been proved by alternative syntheses to be cyanines with a substituted trimethin chain. Similar dyes with an unsubstituted chain have been prepared by condensing pyrroles either with β-ethoxyacraldehyde acetal or with acetal and orthoformic ester in presence of mineral acid. These reactions are general ones for pyrroles containing an imino-group, but there appear to be limitations when the nitrogen atom bears a substituent.

Cyanine dyes have been prepared in which the terminal heterocyclic nuclei have covered a wide range; pyrrole nuclei, however, have not hitherto figured in compounds of this type if the very numerous class of dipyrromethene salts is excepted. The present work to some extent remedies this deficiency, although most of the compounds described below were prepared by an unexpected and novel route.*

The need arose in another connection for certain dipyrromethenes which it was hoped to prepare by the interaction of appropriate α-free pyrroles and ethyl orthoformate in presence of mineral acid. This reaction was readily realised and several applications are described in the present paper. It was noted, however, that the pyrroles gave quite different colours if the condensations were carried out in presence of carbonyl compounds of varied kinds. Thus, when ethyl 4-phenyl-2-methylpyrrole-3-carboxylate was kept in presence of ethyl orthoformate and cold hydrobromic acid, a red crystalline *pyrromethene hydrobromide* (I) was formed, whereas in presence of acetone the solution became intensely blue and scintillating green crystals separated. Compar-

(I.) 

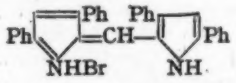
(II.) 

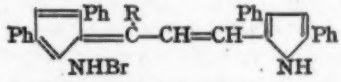
ative experiments indicated that the optimum proportions of reactants were two molecular parts of pyrrole, one molecular part of acetone, and one molecular part of orthoformic ester. Analysis of this and similar com-

* Patent protection pending.

pounds showed that the blue compound was indeed formed by elimination of two molecules of water and three of ethanol with addition of one of hydrogen bromide. Only constitution (II; R = Me) explains these facts satisfactorily and the products must be formulated as *trimethincyanines*. Exactly similar compounds were prepared, in every case in the form of green or steely blue crystals, by replacing acetone by acetophenone, *p*-methoxyacetophenone, β-acetonaphthone, or methyl ethyl ketone; analyses were in good agreement with their formulation as compounds of type (II) where R = an alkyl or aryl residue. Small-scale experiments indicate that the reaction may also be carried out with any mineral acid and *cyclo*pentanone, *cyclo*hexanone, benzyl methyl ketone, propiophenone, chloroacetone, *o*-benzylacetophenone, and indeed with any normal simple ketone containing the group ·CO·CH$_2$·; it failed completely with di*iso*propyl ketone, as would be anticipated from the limitations imposed by the above structure.

These reactions are not limited to the above pyrrole. The more highly arylated 2 : 4-diphenylpyrrole, ethyl orthoformate, and hydrogen bromide in cold acetic acid afforded the red pyrromethene (III); the same reagents with added acetone, however, gave the blue trimethin salt (IV; R = Me), and (IV; R = Ph) arose by the use of acetophenone:

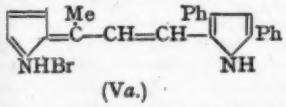
(III.) 

 (IV.)

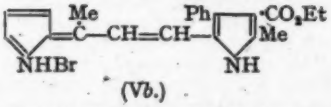
On the other hand, 4-phenyl-2-methyl-, 2 : 4-dimethyl-, 2-triphenylmethyl-pyrrole and even pyrrole itself gave similar colours, so the reaction is clearly a general one for pyrroles which do not bear a substituent on the nitrogen atom.

The structures suggested above are the only possible ones when account is taken of the general properties of the products, analytical data, and the substitution which is permissible without hindering reaction. They were nevertheless confirmed by the following findings:

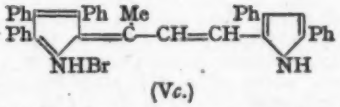
(*a*) 2 : 4-Diphenylpyrrole-5-aldehyde condensed with 2 : 4-diphenylpyrrole, acetone, and hydrobromic acid to give the same product as was obtained from 2 : 4-diphenylpyrrole, acetone, orthoformic ester and hydrobromic acid. Unsymmetrical dyes were similarly prepared from ethyl 4-phenyl-2-methylpyrrole-3-carboxylate, pyrrole, and acetone, from 2 : 4-diphenylpyrrole-5-aldehyde, pyrrole, and acetone, and from 2 : 4-diphenylpyrrole-5-aldehyde, 2 : 3 : 4-triphenylpyrrole and acetone:



(V*a*.)

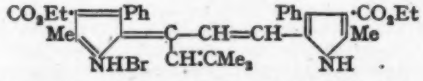


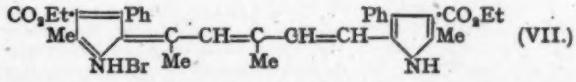
(V*b*.)



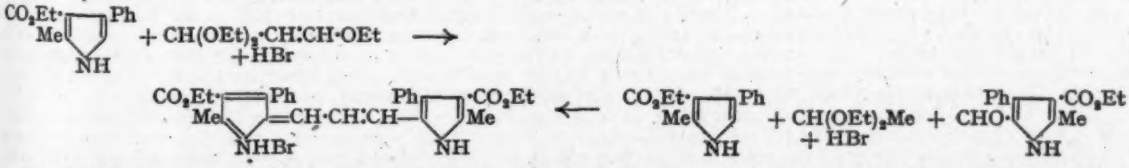
(V*c*.)

(*b*) Pyrroles containing a free α-position condensed with β-ethoxyacraldehyde acetal in presence of mineral acid to give dyes which must contain an unsubstituted trimethin chain. The very similar light absorption of these dyes to that of products obtained by using ketones and orthoformic ester left no doubt that these must contain the same conjugated chain between the nuclei. Ethyl 4-phenyl-2-methylpyrrole-3-carboxylate condensed also with mesityl oxide and ethyl orthoformate. The light absorption showed that the product was again a substituted trimethincyanine (VI) and not the pentamethin compound (VII) which might have arisen:

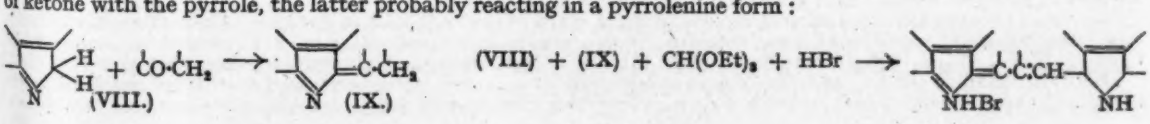
(VI.) 

 (VII.)

The possibility of linking unsubstituted trimethin chains to pyrroles by condensing aldehydes with pyrroles and orthoformic ester was also investigated. Simple tests showed that colours were indeed formed but that reaction was not so ready as with ketones. It was possible, however, to identify the product of interaction of ethyl 4-phenyl-2-methylpyrrole-3-carboxylate, acetal, orthoformic ester and hydrobromic acid with that from the same pyrrole, β-ethoxyacraldehyde acetal and hydrobromic acid:



It might be thought that the reaction between pyrroles, ketone, and orthoformic ester consisted in the intermediate formation of a formyl ketone or a nearly related compound. Formylacetone has been proposed to supply a trimethin chain in linking pyrazolone nuclei (B.P. 515,998) and, as was shown in the present work, it can be used to link pyrrole nuclei. There is, however, evidence to show that the prime reaction is the condensation of ketone with the pyrrole, the latter probably reacting in a pyrrolenine form:



So, although alkylated pyrroles appeared less ready to undergo reaction than arylpyrroles, dye formation was achieved in these cases by first submitting the pyrrole and ketone in presence of mineral acid to moderate heating and then completing condensation with orthoformic ester in the cold. Moreover, in such cases, preliminary condensation was also required even when condensation was completed by standing with a pyrrole-α-aldehyde.

All the preceding compounds differ from other cyanines not only in the heterocyclic systems but also in their containing no *N*-alkyl or *N*-aryl groups. *N*-Phenylpyrrole appeared to react as readily as pyrrole itself with acetone or other ketones and orthoformic ester, but ethyl 4-phenyl-1 : 2-dimethylpyrrole-3-carboxylate has so far failed to give trimethincyanines, although formation of pyrromethene presented no difficulty; there appear to be limitations among *N*-substituted pyrroles, therefore, which remain to be defined.

The absorption spectra of these cyanines present one interesting feature. Trimethincyanines from mono- or di-phenylpyrroles were intensely blue, but those from unsubstituted or more simply substituted pyrroles were shades of red. The colours were practically unaffected by substitution on the trimethin chain, but it is clear that aryl residues in the pyrrole rings have a very pronounced chromophoric effect, which is unexpected in view of the fact that they are only linked and not fused to the heterocyclic residues.

During the course of this work ethyl 4-anisyl-2-methylpyrrole-3-carboxylate, 2-diphenylmethylpyrrole, and ethyl 4-β-naphthyl-2-methylpyrrole-3-carboxylate were prepared by orthodox methods and shown qualitatively to undergo condensation in the same manner as the simpler pyrroles.

Experimental.

2 : 4-*Diphenylpyrrole Cyanines.*—2 : 4-Diphenylpyrrole (2·2 g.) was warmed with ethyl orthoformate (1·65 g.), 50% hydrobromic acid in acetic acid (0·8 c.c.), and acetic acid (20 c.c.) for 1 hour at 100°. *Bis*-2-(3 : 5-*diphenylpyrrole*)*monomethincyanine bromide* (2·0 g.) was filtered from the deep red solution. It separated from ethanol in greenish needles with a brown reflex, m. p. 262° (decomp.) (Found: Br, 15·3. $C_{33}H_{25}N_2Br$ requires Br, 15·1%); light absorption (chloroform), max., 5510 A.

A solution of 2 : 4-diphenylpyrrole (2·2 g.) in ethyl acetate (15 c.c.) was quickly cooled and then treated with acetone (1·5 c.c.) and 1 drop of 5% hydrobromic acid in acetic acid. After 5 mins., ethyl orthoformate (1·65 c.c.), followed by 50% hydrobromic acid in acetic acid (0·81 c.c.), was added and the green dye (0·91 g.) filtered off after 12 hours. *Bis*-2-(3 : 5-*diphenylpyrrole*)-α-*methyltrimethincyanine bromide* separated from ethyl acetate–ether in grass-green plates, m. p. 225° after softening at 215° (Found: C, 75·8; H, 5·3; N, 4·6. $C_{36}H_{29}N_2Br$ requires C, 75·9; H, 5·1; N, 4·9%). The same compound was obtained when 2 : 4-diphenylpyrrole (1·1 g.), acetone (0·35 c.c.), and 50% hydrobromic acid in acetic acid (0·81 c.c.) were warmed on the water-bath for 15 mins., and 2 : 4-diphenylpyrrole-5-aldehyde (1·25 g.) in acetic acid (10 c.c.) added. After 2 hrs. on the water-bath the green crystals were collected and washed with a little chloroform and then with much acetone to remove a little of the dipyrromethene. The residue crystallised from chloroform–acetone in green plates, m. p. 225° after softening at 215°, which gave no depression with the dye previously described (yield, 1·5 g.) (Found: C, 75·8; H, 5·1%). The light absorption (chloroform) of the two preparations was identical; max. 7050 A.

2 : 4-Diphenylpyrrole (2·2 g.), acetophenone (0·6 g.), acetic acid (3 c.c.), and 50% hydrobromic acid in acetic acid (0·81 c.c.) were warmed on the water-bath for 20 mins. Ethyl orthoformate (1·65 c.c.) was then added, and heating continued for 20 mins. more. After standing overnight, the solid was separated from the deep blue solution and washed with methanol to remove a small amount of the dipyrromethene. *Bis*-2-(3 : 5-*diphenylpyrrole*)-α-*phenyltrimethincyanine bromide* crystallised from chloroform in octahedra with a brass-like lustre, m. p. 245° (decomp.) (yield, 1·4 g.) (Found: C, 78·3; H, 5·0; N, 4·7. $C_{41}H_{31}N_2Br$ requires C, 78·0; H, 5·0; N, 4·4%). Light absorption (chloroform): max. 7050 A.

Freshly distilled pyrrole (0·35 g.), acetone (0·35 c.c.), acetic acid (10 c.c.), and 50% hydrobromic acid in acetic acid (0·81 c.c.) were warmed together, 2 : 4-diphenylpyrrole-5-aldehyde (1·25 g.) in acetic acid (10 c.c.) then added, and the whole warmed gently on the water-bath for 2 hrs. 2-*Pyrrole*-2′-(3′ : 5′-*diphenylpyrrole*)-α-*methyltrimethincyanine bromide* (V*a*) separated when the intensely purple solution was poured into water. The dye, crystallised from methanol–ether, decomposed above 300° without melting (Found: C, 68·9; H, 4·9. $C_{24}H_{21}N_2Br$ requires C, 69·1; H, 5·1%); light absorption (chloroform), max. 6080 A.

2 : 3 : 4-Triphenylpyrrole (1·5 g.) was condensed with acetone (0·35 c.c.) in acetic acid (11 c.c.) containing hydrobromic acid (0·4 g.) for 5 minutes on a water-bath; 2 : 4-diphenylpyrrolealdehyde (1·25 g.) in acetic acid (10 c.c.) was added, and the solution warmed for 1 hour. The blue solution was poured into water, and the precipitated dye crystallised from methanol. 2-(3 : 4 : 5-*Triphenylpyrrole*)-2′-(3′ : 5′ : *diphenylpyrrole*)-α-*methyltrimethincyanine bromide* (V*c*) separated in green needles, m. p. 148° (Found: C, 78·1; H, 5·3. $C_{42}H_{33}N_2Br$ requires C, 78·1; H, 5·2%).

4-*Phenyl*-2-*methylpyrrole Cyanines.*—Ethyl 4-phenyl-2-methylpyrrole-3-carboxylate (2·3 g.) in boiling acetic acid (10 c.c.) was treated with ethyl orthoformate (1·65 g.) and 50% hydrobromic acid in acetic acid (0·8 c.c.). After 2 hours, the orange needles were collected, washed with acetic acid, and recrystallised from ethanol. *Bis*-2-(4-*carbethoxy*-3-*phenyl*-5-*methylpyrrole*)*monomethincyanine bromide* formed long oranges needles with a blue reflex, m. p. 196° (Found: C, 63·3; H, 5·3. $C_{29}H_{29}O_4N_2Br$ requires C, 63·4; H, 5·3%); light absorption (chloroform), max., 4890 A.

Ethyl 4-phenyl-2-methylpyrrole-3-carboxylate (1·15 g.), acetone (0·7 c.c.) and ethyl orthoformate (1·65 c.c.) were mixed with glacial acetic acid (3 c.c.) and treated with 50% hydrobromic acid in acetic acid (1 c.c.). After 12 hours the deep blue solution deposited a green felt of needles, which was collected and washed with methanol and with ether. *Bis*-2-(4-*carbethoxy*-3-*phenyl*-5-*methylpyrrole*)-α-*methyltrimethincyanine bromide* separated from formic acid in matted grass-green needles (0·5 g.), m. p. 198° (decomp.) (Found: C, 65·4; H, 5·8; N, 4·6. $C_{32}H_{33}O_4N_2Br$ requires C, 65·2; H, 5·6; N, 4·7%); light absorption (chloroform), max. 6090 A.

Bis-2-(4-*carbethoxy*-3-*phenyl*-5-*methylpyrrole*)-α-*ethyltrimethincyanine bromide*, obtained similarly from methyl ethyl ketone, formed matted green needles, m. p. 199°, separating from formic acid (Found: C, 65·9; H, 6·0. $C_{33}H_{35}O_4N_2Br$ requires C, 65·7; H, 5·9%); light absorption (chloroform), max. 6100 A.

By using an equivalent quantity of mesityl oxide in place of acetone, *bis*-2-(4-*carbethoxy*-3-*phenyl*-5-*methylpyrrole*)-α-iso*butenyltrimethincyanine bromide* was obtained; it separated in long green rods, m. p. 212°, from formic acid (Found: C, 66·9; H, 6·1. $C_{35}H_{37}O_4N_2Br$ requires C, 66·8; H, 5·9%); light absorption (chloroform), max. 6100 A.

Methylformanilide (12 c.c.) and phosphorus oxychloride (52 c.c.) were mixed and kept for 1 hour and then cooled to 0·5°. Ethyl 4-phenyl-2-methylpyrrole-3-carboxylate (21 g.) was slowly added, and the mixture stirred for 2 hours.

Decomposition with water gave *3-carbethoxy-4-phenyl-2-methylpyrrole-5-aldehyde*, which separated in needles, m. p. 149°, from light petroleum (Found: C, 69·8; H, 5·8. $C_{15}H_{15}O_3N$ requires C, 70·0; H, 5·9%).

Ethyl 4-phenyl-2-methylpyrrole-3-carboxylate (1·15 g.) in acetic acid (5 c.c.) was treated with acetal (0·6 c.c.) and 50% hydrobromic acid in acetic acid (0·8 c.c.) at 20°. After 5 minutes the preceding aldehyde (1·3 g.) in acetic acid (5 c.c.) was added. On standing, green prisms of *bis-2-(4-carbethoxy-3-phenyl-5-methylpyrrole)trimethincyanine bromide*, m. p. 199°, appeared. The same compound was obtained by warming the same pyrrole (1·15 g.), β-ethoxyacraldehyde-acetal (0·45 g.), and 10% hydrobromic acid in acetic acid (6 c.c.). On standing the dye separated; it was washed with methanol and with ethyl formate and finally crystallised from formic acid to form prisms, m. p. 200°, giving no depression with the compound prepared previously (Found: C, 64·5; H, 5·3. $C_{31}H_{31}O_4N_2Br$ requires C, 64·6; H, 5·4%); light absorption (chloroform), max. 6010 A.

Pyrrole (0·35 g.), acetone (0·35 c.c.), and acetic acid (11 c.c.) containing hydrobromic acid (0·5 g.) were warmed together for 15 minutes, and the solution treated with 3-carbethoxy-4-phenyl-2-methylpyrrole-5-aldehyde (1·25 g.) in acetic acid (10 c.c.). After 2 hours on a water-bath the brilliant red solution was poured into water and *2-pyrrole-2′-(3′-carbethoxy-4′-phenyl-5′-methylpyrrole)-α-methyltrimethincyanine bromide* (Vb) was collected. It had m. p. above 300° and was purified by solution in methanol and precipitation with ether (Found: C, 61·7; H, 5·5. $C_{32}H_{33}O_4N_2Br$ requires C, 61·8; H, 5·4%); light absorption (chloroform), max. 5060 A.

The same pyrrole (2·3 g.), acetophenone (1·2 g.), acetic acid (5 c.c.), and 50% hydrobromic acid in acetic acid (1·6 c.c.) were warmed on the steam-bath for 20 mins., and then treated with a further quantity of the pyrrole (2·3 g.), ethyl orthoformate (1·65 g.), and acetic acid (5 c.c.). A deep blue-green colour appeared at once and needles began to separate. After 12 hours these were collected and recrystallised from ethyl formate. *Bis-2-(4-carbethoxy-3-phenyl-5-methylpyrrole)-α-phenyltrimethincyanine bromide* separated in green needles, m. p. 202° (decomp.) (Found: C, 68·4; H, 5·5. $C_{37}H_{35}O_4N_2Br$ requires C, 68·2; H, 5·4%). Light absorption (chloroform): max. 6180 A.

When the same pyrrole (1·15 g.), β-naphthyl methyl ketone (0·8 g.), acetic acid (5 c.c.), ethyl orthoformate (1·5 c.c.) and 50% hydrobromic acid in acetic acid (1 c.c.) were brought together, vigorous reaction set in. The green crystalline product (1·0 g.) was recrystallised from ethyl formate. *Bis-2-(4-carbethoxy-3-phenyl-5-methylpyrrole)-α-2′-naphthyltrimethincyanine bromide* separated in needles, m. p. 186° (Found: C, 70·2; H, 5·4. $C_{41}H_{37}O_4N_2Br$ requires C, 70·2; H, 5·3%); light absorption (chloroform), max. 6210 A.

Bis-2-(4-carbethoxy-3-phenyl-5-methylpyrrole)-α-p-methoxyphenyltrimethincyanine bromide, prepared similarly from *p*-methoxyacetophenone, separated from formic acid in green needles, m. p. 210° (Found: C, 67·3; H, 5·4; N, 4·1. $C_{38}H_{37}O_5N_2Br$ requires C, 67·0; H, 5·4; N, 4·1%); light absorption (chloroform), max. 6200 A.

4-Phenyl-2-methylpyrrole (1·57 g.), acetophenone (0·6 g.), and 50% hydrobromic acid in acetic acid (0·8 c.c.) were mixed to a homogeneous product at 40°, and ethyl orthoformate (1·65 c.c.) added. On standing, a mixture of dark green octahedra and yellow prisms formed and was separated by washing with ethyl formate. The residual *bis-2-(3-phenyl-5-methylpyrrole)-α-phenyltrimethincyanine bromide*, crystallised from ethyl formate, had m. p. 221° (Found: C, 74·6; H, 5·1. $C_{31}H_{27}N_2Br$ requires C, 74·5; H, 5·1%); light absorption (chloroform), max. 6210 A.

2:4-Dimethylpyrrole (0·5 g.), acetophenone (0·6 g.), and 5% hydrobromic acid in acetic acid (10 c.c.) were warmed at 100° for 15 minutes and then treated with the same pyrrole (0·5 g.), acetic acid (5 c.c.), and ethyl orthoformate (1·65 g.). After warming for 2 hours, the blue solution was poured into water, and the dye collected and crystallised from toluene–light petroleum. *Bis-2-(3:5-dimethylpyrrole)-α-phenyltrimethincyanine bromide* formed black crystals with a copper-like sheen, m. p. above 300° (Found: C, 65·7; H, 6·1. $C_{21}H_{23}N_2Br$ requires C, 65·8; H, 6·05%); light absorption (chloroform), max. 5990 A.

Miscellaneous Pyrroles and their Derivatives.—ω-Amino-*p*-methoxyacetophenone hydrochloride (22·7 g.), anhydrous sodium acetate (15·4 g.), ethyl acetoacetate (16 c.c.), water (20 c.c.), and acetic acid (83 c.c.) were heated on the water-bath for 1 hour and then poured into ice-water (1 l.). The precipitate (20 g.) was crystallised from dilute ethanol and from light petroleum. *Ethyl 4-anisyl-2-methylpyrrole-3-carboxylate* formed needles m. p. 124°, which sublimed in a high vacuum (Found: C, 69·9; H, 6·9. $C_{15}H_{17}O_3N$ requires C, 69·5; H, 6·5%).

Pyrrole (6·7 g.), diphenylcarbinol (9·2 g.), and acetic acid (50 c.c.) were heated to boiling, and potassium hydrogen sulphate (13·6 g.) added. After the vigorous reaction, the product was cooled and crude *2-diphenylmethylpyrrole* was collected; it was purified by distillation at 100° in a high vacuum and crystallisation from light petroleum, being then obtained in long columns, m. p. 267° (Found: C, 87·7; H, 6·35. $C_{17}H_{15}N$ requires C, 87·55; H, 6·5%).

ω-Chloro-β-acetonaphthone (75 g.) in chloroform (100 c.c.) was kept with hexamine (30 g.) in the same solvent (100 c.c.) for 1 day. The cream-coloured solid (80 g.) was collected and kept for 3 days with ethanol (500 c.c.) and concentrated hydrochloric acid (72 c.c.); ammonium chloride was then removed, and the filtrate evaporated to dryness. The residue was crystallised from hot water and finally from acetic acid to give *ω-amino-β-acetonaphthone hydrochloride*, m. p. 248° (Found: C, 65·1; H, 5·5. $C_{12}H_{12}ONCl$ requires C, 65·2; H, 5·4%).

The preceding amino-compound (11 g.) was heated for 1 hour on the steam-bath with anhydrous sodium acetate (4 g.), ethyl acetoacetate (6·5 g.), and acetic acid (100 c.c.) and then poured on ice. The precipitate was distilled in a high vacuum, and the distillate crystallised from light petroleum (b. p. 100—120°); *ethyl 4-β-naphthyl-2-methylpyrrole-5-carboxylate* formed needles, m. p. 114° (Found: C, 77·5; H, 6·3. $C_{18}H_{17}O_2N$ requires C, 77·4; H, 6·1%).

Ethyl 4-phenyl-2-methylpyrrole-3-carboxylate (1·2 g.) was ground with benzotrichloride (1·0 g.), and the mixture heated for 1 hour at 100°. The intense purple product was cooled and poured into water, and the solid triturated with aqueous ammonia and ethanol. The light base, *bis-2-(4-carbethoxy-3-phenyl-5-methylpyrrole)-α-phenylmonomethincyanine*, crystallised from ethanol in needles (0·5 g.), m. p. 226° (Found: C, 77·4; H, 5·9. $C_{35}H_{32}O_4N_2$ requires C, 77·3; H, 5·9%).

Ethyl 4-phenyl-2-methylpyrrole-3-carboxylate (11·5 g.) was stirred at 0° with ether (100 c.c.) and excess of dry sodium carbonate while bromine (2·5 c.c.) in a little ether was added dropwise; stirring was then continued for 15 mins., and the solution filtered and evaporated in a stream of nitrogen and eventually in a vacuum. The residue was crystallised repeatedly from light petroleum to give *ethyl 5-bromo-4-phenyl-2-methylpyrrole-3-carboxylate* as pale yellow octahedra, m. p. 120°, which readily blackened on standing in air or heating (Found: C, 54·7; H, 4·2. $C_{14}H_{14}O_2NBr$ requires C, 54·6; H, 4·6%).

Ethyl 4-phenyl-2-methylpyrrole-3-carboxylate (1·2 g.) in acetic acid (5 c.c.) at 50° was treated with 40% formalin (1 c.c.). After 1 hour the precipitate was collected and recrystallised from ethanol; *bis-2-(4-carbethoxy-3-phenyl-5-methylpyrryl)methane* formed slender needles (0·4 g.), m. p. 231° (Found: C, 74·0; H, 6·3. $C_{29}H_{30}O_4N_2$ requires C, 74·1; H, 6·4%).

Ethyl 4-phenyl-2-methylpyrrole-3-carboxylate (4·5 g.) in acetic acid (40 c.c.) was added as rapidly as possible to bromine (2·5 c.c.) in acetic acid (15 c.c.). After standing overnight, the purple solution was cooled until it was semi-solid, then filtered, and the acetic acid removed with cold water. The residual dye was chromatographed in chloroform on alumina and then precipitated from chloroform with light petroleum. *2-(3-Carbethoxy-4-phenylpyrrole)-2′-(3′-carbethoxy-4′-phenyl-5′-methylpyrrole)monomethincyanine bromide* crystallised from light petroleum in red needles, m. p. 160° (decomp.);

it gave a bromine-free base on trituration with aqueous ammonia and an intensely yellow fluorescent solution in chloroform, especially in ultra-violet light (Found: C, 63·3; H, 5·1. $C_{28}H_{27}O_4N_2Br$ requires C, 62·9; H, 5·1%).

The authors thank Prof. I. M. Heilbron, D.S.O., F.R.S., for his interest and encouragement and Imperial Chemical Industries, Ltd., Dyestuffs Division, for gifts of chemicals.

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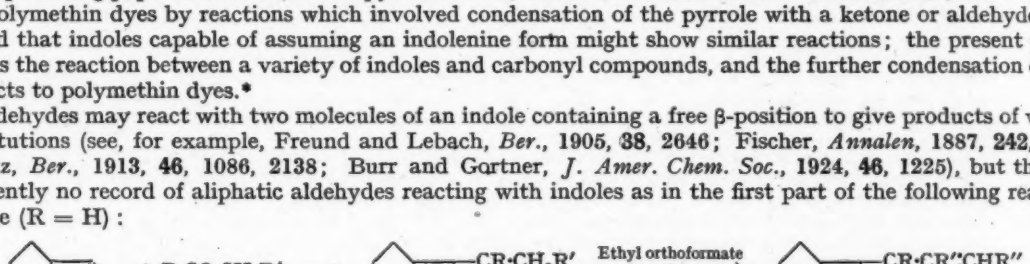
132. *Preparation of Indole Trimethincyanines.*

By A. H. COOK and J. R. MAJER.

Representative indoles containing unsubstituted NH- and β-positions have been condensed with ketones and β-keto-esters to give indolylidene bases or salts thereof. Those bases or salts containing the groups :C·CH_2R (R = H, hydrocarbon residue, or CO_2Et) condense further with appropriate heterocyclic aldehydes to yield trimethincyanines.

IN the preceding paper it was shown that pyrroles could, within certain limitations of substitution, be converted into polymethin dyes by reactions which involved condensation of the pyrrole with a ketone or aldehyde. It seemed that indoles capable of assuming an indolenine form might show similar reactions; the present paper records the reaction between a variety of indoles and carbonyl compounds, and the further condensation of the products to polymethin dyes.*

Aldehydes may react with two molecules of an indole containing a free β-position to give products of varied constitutions (see, for example, Freund and Lebach, *Ber.*, 1905, **38**, 2646; Fischer, *Annalen*, 1887, **242**, 372; Scholtz, *Ber.*, 1913, **46**, 1086, 2138; Burr and Gortner, *J. Amer. Chem. Soc.*, 1924, **46**, 1225), but there is apparently no record of aliphatic aldehydes reacting with indoles as in the first part of the following reaction scheme (R = H):



(I.) (II.)

Similarly there appear to be no known reactions of ketones (R = hydrocarbon residue) of the desired type, although Scholtz (*loc. cit.*) described the condensation of 2-methylindole with ethyl acetoacetate to give the corresponding ethyl β-indolylidenebutyrate and other condensations between indoles and ketones. Consequently, although the formation of indomethenes from indoles and ethyl orthoformate is known (König, *J. pr. Chem.*, 1911, **84**, 217), it was not surprising that the method of the previous paper failed when applied to indoles in spite of the brilliant colours which were sometimes observed; the formation of indomethenes appeared to be so rapid that mixtures of dyes were formed and the isolation of the desired trimethin compounds was not accomplished.

However, it was shown that indoles carrying a free β-position condense regularly with β-keto-esters to give stable indolylidene esters or salts thereof to which constitutions of type (I) (R′ = CO_2Et) must be assigned. Crystalline salts were obtained from the following combinations: 2-methylindole and ethyl formylacetate; 7-methylindole and ethyl acetoacetate; 2-methylindole and ethyl benzoylacetate. There was good evidence that 2-phenylindole undergoes condensation but 2-phenyl-1-methylindole was unreactive. Under similar conditions indole or 2-methylindole failed to react with ethyl lævulate or ethyl acetonedicarboxylate.

Most of these condensation products gave polymethin dyes on reaction with appropriate heterocyclic aldehydes. Crystalline dyes were obtained, for example, from indolylidene esters, with limitations mentioned below, and 2-methylindole-3-aldehyde and 3-carbethoxy-4-phenyl-2-methylpyrrole-5-aldehyde. Intense colours were obtained with 1 : 3 : 3-trimethyl-2-methylindoline-ω-aldehyde, but no crystalline product was isolated. Attempted condensations with 1 : 3 : 3-trimethyl-2-anilinovinylindoline iodide and similar compounds were also unsuccessful. The constitution of the dyes so obtained is in no doubt for the following facts:

(*a*) Dye formation was independent of substitution in the 2-position of the indole nucleus and must have been due to reactivity of part of the substituent in the 3-position.

(*b*) Dye formation proceeded as easily with condensation products of ethyl benzoylacetate as with ethyl acetoacetate but failed when the indolylidene ester was derived from ethyl α-methylacetoacetate; elimination of water must take place, therefore, between the heterocyclic aldehyde and the methylene adjacent to the ester group as in (II) (R′ = CO_2Et). The deep colour and absorption measurements confirm the polymethin nature of the dyes.

These results suggested possible success by replacing the ketoesters by ketones or aldehydes. In presence of a large excess of carbonyl compound and mineral acid, β-free indoles afforded crystalline salts of bases undoubtedly of constitution (I; R = hydrocarbon residue, R′ = H or hydrocarbon residue). Compounds of this type were prepared in pure condition from 2-methylindole and acetone, methyl ethyl ketone, or *cyclo*pentanone. Where the original carbonyl compound contained the group CO·CH_2, the condensation product reacted with heterocyclic aldehydes and from the deep colour of the resulting dyes it must be concluded that they also are of constitution (II) (R = a hydrocarbon residue, R′ = H or hydrocarbon residue). Paraldehyde

* Patent protection pending.

was used with 2-methylindole, to provide a cyanine with an unsubstituted trimethin chain, though the intermediate indolenine was not isolated.

Alkylation of the nitrogen atoms is clearly desirable, but so far this has proved impossible both in the case of the dyes themselves and of the intermediates. In the case of ethyl β-2-methylindolylidenebutyrate extended efforts were made to effect quaternisation, but the ester was surprisingly resistant. It failed to react even after prolonged treatment with methyl iodide at an elevated temperature; methyl sulphate had no action at room temperature and gave only oily, apparently decomposition, products on heating. In other ways also the ester was less reactive than might have been anticipated and failed to yield the expected anilide by the usual methods from aniline in xylene, or in presence of pyridine or phosphorus oxychloride; the anilide was not obtained on heating 2-methylindole with acetoacetanilide.

Experimental.

3-Indolylidene. Esters.—2-Methylindole (2 g.) in ethanol (20 c.c.) was triturated with ethyl sodioformylacetate (2 g.) and treated dropwise with concentrated hydrochloric acid (5 c.c.) at 0°. After 3 days the solution was diluted with water, and the precipitate taken up in chloroform and chromatographed on alumina. *Ethyl β-2-methyl-3-indolylidenepropionate*, recovered from the filtrate, crystallised from benzene–light petroleum in pale yellow needles, m. p. 80° (Found: N, 6·0. $C_{14}H_{15}O_2N$ requires N, 6·1%).

7-Methylindole (2 g.) in ethanol (10 c.c.) was treated with ethyl acetoacetate (5 c.c.) and concentrated hydrochloric acid (5 c.c.). Heat was evolved and after 30 mins. the crystalline deposit was collected, treated with a little aqueous ammonia, and recrystallised from ethanol. *Ethyl β-7-methyl-3-indolylidenebutyrate* (yield, 1·5 g.) formed needles, m. p. 188°, which became red in the air (Found: C, 74·3; H, 6·8. $C_{15}H_{17}O_2N$ requires C, 74·1; H, 7·0%).

Ethyl β-phenyl-β-2-methyl-3-indolylidenepropionate was prepared similarly from 2-methylindole (2 g.), ethyl benzoylacetate (5 c.c.), ethanol (10 c.c.), and concentrated hydrochloric acid (5 c.c.). The crude product (2·5 g.) was collected after 3 days and repeatedly crystallised from ethanol to give pale yellow needles, m. p. 143° (Found: N, 4·7. $C_{19}H_{19}O_2N$ requires N, 4·6%).

Ethyl β-3-indolylidenebutyrate, prepared similarly, crystallised from ethanol in needles, m. p. 180° (decomp.) (Found: N, 6·2. $C_{14}H_{15}O_2N$ requires N, 6·1%).

3-Alkylideneindoles.—2-Methylindole (1·3 g.) in acetone (5 c.c.) was treated at 0° with concentrated sulphuric acid (0·55 c.c.) with vigorous shaking. Heat was evolved and, on cooling, the thick, bright yellow salt was collected and crystallised from acetic acid. *2-Methyl-3-isopropylideneindolenine sulphate* was obtained as yellow needles, m. p. 165° (decomp.), which slowly darkened in moist air (Found: N, 5·2; S, 11·7. $C_{13}H_{15}O_4NS$ requires N, 5·3; S, 11·9%). Similarly prepared were: *2-Methyl-3-isobutylideneindolenine sulphate*, separating in yellow needles, m. p. 89°, from acetic acid (Found: N, 4·9; S, 11·1. $C_{13}H_{17}O_4NS$ requires N, 5·0; S, 11·4%), and *2-methyl-3-cyclopentylideneindolenine sulphate*, yellow needles, m. p. 153° (decomp.) after previous darkening, from acetic acid (Found: N, 4·9; S, 11·0. $C_{14}H_{17}O_4NS$ requires N, 4·75; S, 10·85%).

Dyes derived from Indolenine Esters.—A solution of ethyl 2-methyl-3-indolylidenebutyrate (1·2 g.) and 3-carbethoxy-4-phenyl-2-methylpyrrole-5-aldehyde (1·3 g.) in acetic acid (15 c.c.) was heated to boiling, and 50% hydrobromic acid in acetic acid (0·8 c.c.) added. After the vigorous reaction had abated, the solution was poured into excess of dilute aqueous ammonia, and the pale brown solid collected. [*2-Methyl-3-indole*]-[*4-carbethoxy-3-phenyl-5-methyl-2-pyrrole*]-*β-carbethoxy-α-methyltrimethincyanine* separated from light petroleum as a yellow microcrystalline solid, m. p. 154° (Found: C, 75·1; H, 6·3. $C_{30}H_{30}O_4N_2$ requires C, 74·8; H, 6·2%). It was yellow in ethanol, becoming deep magenta on addition of acid. Light absorption (ethanol–hydrogen chloride): max. 5850 A.

The same indolylidene ester was condensed similarly with 2-methylindole-3-aldehyde. When the reaction mixture was kept overnight, *bis-*[*2-methyl-3-indole*]-*β-carbethoxy-α-methyltrimethincyanine bromide* separated in copper-coloured needles, m. p. 202° (decomp.) after recrystallisation from acetic acid (Found: N, 6·2; Br, 16·8. $C_{31}H_{35}O_2N_2Br$ requires N, 6·1; Br, 17·2%). The dye was deep purple in ethanol and the colour was reversibly discharged by alkali. Light absorption (ethanol): max. 5780 A. *Bis-*[*2-methyl-3-indole*]-*β-carbethoxy-α-phenyltrimethincyanine* was obtained similarly. It crystallised on cooling from the purple-red reaction medium and, recrystallised from acetic acid, formed steel-blue needles with a coppery reflex, m. p. 230° (Found: C, 67·9; H, 5·0. $C_{30}H_{17}O_2N_2Br$ requires C, 68·2; H, 5·1%). Light absorption, max. 5890 A.

Dyes derived from Alkylideneindolenines.—A mixture of 2-methylindole-3-aldehyde (0·8 g.), 2-methyl-3-*iso*propylideneindolenine sulphate (1·44 g.), and acetic acid (10 c.c) was refluxed for 30 mins. and cooled overnight. The long green needles were collected and recrystallised from acetic acid. *Bis-*[*2-methyl-3-indole*]-*α-methyltrimethincyanine sulphate* had m. p. 168° (decomp.) and gave a purple-red solution in ethanol (Found: N, 6·7; S, 7·8. $C_{23}H_{22}O_4N_2S$ requires N, 6·8; S, 7·8%). Light absorption (ethanol): max. 5790 A.

Indole (1·17 g.) in acetone (3 c.c.) was treated with concentrated sulphuric acid (0·55 c.c.). After the reaction, the excess of acetone was removed in a vacuum, 2-methylindole-3-aldehyde (1·6 g.) and acetic acid (10 c.c.) added, and the whole warmed on the water-bath for 30 mins. The solution was poured into aqueous potassium iodide, and the dye purified by repeated precipitation from acetic acid with ether. *3-Indole-3′-(2′-methylindole)-α-methyltrimethincyanine iodide* formed a dark microcrystalline powder, m. p. 122° (decomp.), giving a deep red solution in ethanol (Found: I, 29·4. $C_{21}H_{19}N_2I$ requires I, 29·8%). Light absorption (ethanol): max. 5810 A.

2-Methylindole (1·3 g.) in paraldehyde (5 c.c.) was cooled with solid carbon dioxide until the paraldehyde was just solidifying, and concentrated sulphuric acid (0·55 c.c.) added slowly with shaking. The yellow solid was quickly collected, dissolved in acetic acid (15 c.c.), and treated with 2-methylindole-3-aldehyde (1·6 g.), and the whole boiled for 1 hr. On cooling, the crystals were collected and recrystallised from acetic acid. *Bis-*3-[*2-methylindole*]*trimethincyanine sulphate* decomposed above 300° (Found: N, 7·2; S, 7·9. $C_{21}H_{20}O_4N_2S$ requires N, 7·1; S, 8·1%). Light absorption (ethanol): max. 5550 A.

2-Methyl-3-*cyclo*pentylideneindolenine sulphate (1·5 g.) was heated on the water-bath for 30 mins. in acetic acid (10 c.c.) containing 3-carbethoxy-4-phenyl-2-methylpyrrole-5-aldehyde (1·3 g.). The purple-blue solution was diluted with ether, and the dye purified by precipitation with ether from acetic acid. [*2-Methyl-3-indole*]-[*4-carbethoxy-3-phenyl-5-methyl-2-pyrrole*]-*αβ-trimethylenetrimethincyanine sulphate* decomposed above 300° (Found: N, 5·6; S, 6·0. $C_{28}H_{28}O_4N_2S$ requires N, 5·3; S, 6·0%). Light absorption (ethanol): max. 6960 A.

The authors thank Professor I. M. Heilbron, D.S.O., F.R.S., for his interest and encouragement and Imperial Chemical Industries Ltd., Dyestuffs Division, for grants and gifts of chemicals.

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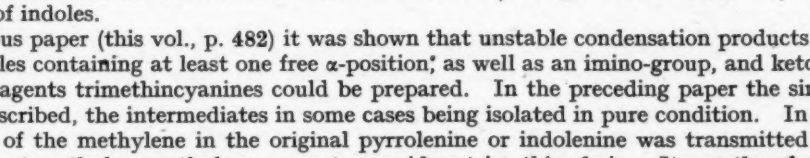
133. *An Extension of the Ehrlich Reaction.*

By A. H. Cook and J. R. Majer.

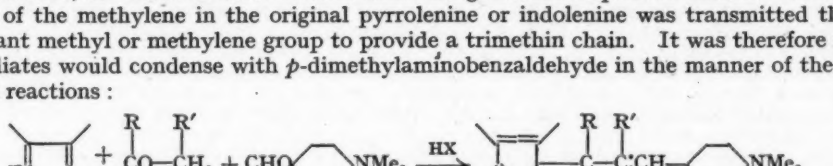
Pyrroles containing a free α-position and indoles with a free β-position have been condensed with ketones and *p*-dimethylaminobenzaldehyde to give blue dyes. The formulation of the products as trimethincyanines was confirmed by an alternative synthesis of a representative dye.

The Ehrlich reaction, *i.e.*, production of a deep red colour when pathological urine containing urobilinogen is treated with *p*-dimethylaminobenzaldehyde in acid solution in the cold, has long been known to be exhibited by all pyrrole compounds containing a free or potentially free α-position. The colour is due to equimolecular condensation of aldehyde with the pyrrolenine form of the pyrrole (Fischer-Orth, "Die Pyrrole," I, 66). Similar red colours form the basis of the Salkowski reaction (*Biochem. Z.*, 1919, **97**, 124) and its variants for the detection of indoles.

In a previous paper (this vol., p. 482) it was shown that unstable condensation products could be obtained between pyrroles containing at least one free α-position, as well as an imino-group, and ketones; with further appropriate reagents trimethincyanines could be prepared. In the preceding paper the similar behaviour of indoles was described, the intermediates in some cases being isolated in pure condition. In all these reactions the reactivity of the methylene in the original pyrrolenine or indolenine was transmitted through a double bond to a distant methyl or methylene group to provide a trimethin chain. It was therefore anticipated that these intermediates would condense with *p*-dimethylaminobenzaldehyde in the manner of the simpler Ehrlich and Salkowski reactions:

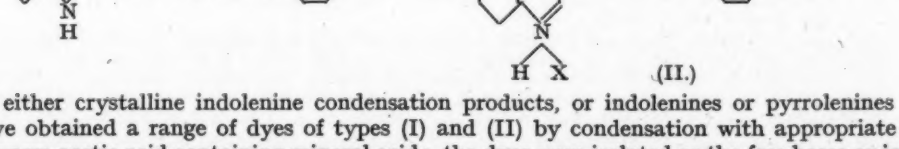


(I.)

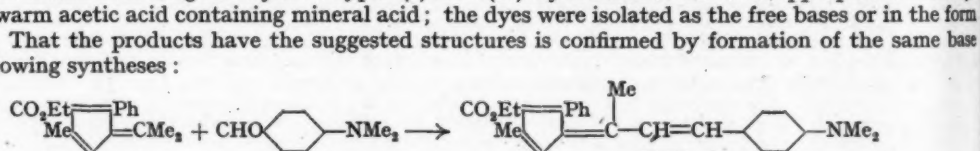


(II.)

Employing either crystalline indolenine condensation products, or indolenines or pyrrolenines prepared *in situ*, we have obtained a range of dyes of types (I) and (II) by condensation with appropriate carbonyl compounds in warm acetic acid containing mineral acid; the dyes were isolated as the free bases or in the form of their salts. That the products have the suggested structures is confirmed by formation of the same base (III) in the following syntheses:



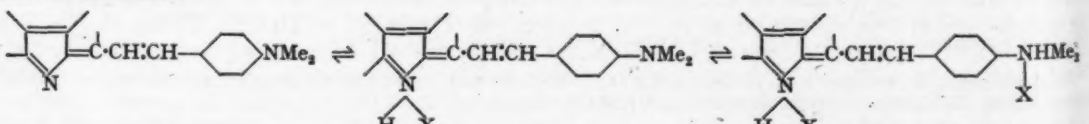
(III.)



(IV.)

Similarly, condensation of 3-carbethoxy-4-phenyl-2-methylpyrrole with *p*-dimethylaminocinnamaldehyde afforded (IV), but attempts to condense the pyrrole and acetaldehyde, or paraldehyde, with *p*-dimethylaminobenzaldehyde were fruitless.

In view of the instability of the products of the Ehrlich reaction, the present dyes were surprisingly stable, and the salts as well as the bases could be purified by chromatography on alumina. The salts were all deep indigo-blue in solution, absorbing in the far red part of the visible spectrum. The behaviour of the dyes towards acids and alkalis, however, was similar to that of the Ehrlich dyes: *e.g.*, the colours faded reversibly in presence of excess acid or alkali; by analogy with the Erhlich dyes this must be attributed to the formation of base or acid salts:



Pale yellow. Blue. Pale yellow.

Experimental.

(For brevity, "aldehyde" throughout implies *p*-dimethylaminobenzaldehyde.)

Condensations between Pyrroles, Ketones, and Aldehyde.—Pyrrole (0·7 g.), acetone (0·7 c.c.), and acetic acid (30 c.c.) containing hydrobromic acid (0·8 g.) were mixed, and after 2—3 mins. aldehyde (1·5 g.) in a little acetic acid was added. After 2 hours on the steam-bath the purple solution was diluted with water and the dye crystallised from methanol–ether; [2-*pyrrole*]-[4-*dimethylaminobenzene*]-α-*methyltrimethincyanine bromide* (I; R = Me, R′ = H, X = Br) formed a dark brown powder decomposing above 300° (Found: C, 60·4; H, 6·3. $C_{16}H_{19}N_2Br$ requires C, 60·2; H, 6·0%). In similar manner 2 : 4-dimethylpyrrole (0·95 g.), acetone (0·7 c.c.), and aldehyde (1·5 g.) were condensed in acetic acid (24 c.c.) containing hydrobromic acid (0·8 g.), and reaction completed during 1 hour at 100°. Dilution of the deep blue solution and crystallisation of the precipitate from acetic acid–ether gave [3 : 5-*dimethyl*-2-*pyrrole*]-[4-*dimethylaminobenzene*]-α-*methyltrimethincyanine bromide*, m. p. 257° (decomp.) (Found: C, 62·6; H, 6·4. $C_{18}H_{23}N_2Br$ requires C, 62·3; H, 6·6%). By replacing acetone by the equivalent quantity of acetophenone, [3 : 5-*dimethyl*-2-*pyrrole*]-[4-*dimethylaminobenzene*]-α-*phenyltrimethincyanine bromide* (I; R = Ph, R′ = H, X = Br) was prepared (yield 90%); it crystallised from acetic acid–ether, and decomposed above 300° (Found: Br, 19·5. $C_{23}H_{25}N_2Br$ requires Br, 19·6%). 3-Carbethoxy-4-phenyl-2-methylpyrrole (2·3 g.) was condensed with acetone (0·7 c.c.) in acetic acid (16 c.c.) containing hydrobromic acid (0·8 g.) and then with aldehyde (1·5 g.) in acetic acid for 1 hour. On pouring the mixture into dilute ammonia [4-*carbethoxy*-3-*phenyl*-5-*methyl*-2-*pyrrole*]-[4-*dimethylaminobenzene*]-α-*methyltrimethincyanine bromide* (III) was precipitated; it crystallised from light petroleum and had m. p. 182° (Found: C, 82·7; H, 7·0; N, 7·2. $C_{28}H_{29}O_2N_2$ requires C, 83·0; H, 7·2; N, 7·0%). The same compound was obtained by heating 3-carbethoxy-4-phenyl-2-methylpyrrole (2·3 g.) with *p*-dimethylaminobenzylideneacetone (1·5 g.) in acetic acid (15 c.c.) containing hydrobromic acid (0·4 g.) to boiling for 1 hour and pouring the blue solution into ammonia. On similarly condensing the same pyrrole (2·3 g.) with *p*-dimethylaminocinnamaldehyde (1·3 g.) and pouring the solution in acetic acid into ether, [4-*carbethoxy*-3-*phenyl*-5-*methyl*-2-*pyrrole*]-[4-*dimethylaminobenzene*]*trimethincyanine bromide* (IV) was obtained. After purification by repeated precipitation from acetic acid with ether, it formed a black powder, decomposing above 300° (Found: Br, 17·0. $C_{25}H_{27}O_2N_2Br$ requires Br, 17·1%). On condensing 2-diphenylmethylpyrrole (2·3 g.) with acetone (0·7 c.c.) in acetic acid (20 c.c.), hydrobromic acid (0·8 g.), and aldehyde (1·5 g.) for 1 hour at 100° and pouring the deep blue solution into ammonia, [5-*diphenylmethyl*-2-*pyrrole*]-[4-*dimethylaminobenzene*]-α-*methyltrimethincyanine* was obtained; it crystallised from acetone–ether and decomposed above 300° without melting (Found: C, 85·95; H, 7·0. $C_{29}H_{29}N_2$ requires C, 86·1; H, 7·0%).

Condensations between Indoles, Ketones, and Aldehyde.—Ethyl 2-methylindolylidenebutyrate (1·0 g.) and aldehyde (0·65 g.) were dissolved in boiling acetic acid (10 c.c.) containing hydrobromic acid (0·25 g.), and the mixture allowed to cool. The deep blue solution was poured into dilute ice-cold ammonia, and the precipitate (yield quantitative) collected. Several crystallisations from a mixture of benzene and light petroleum gave [2-*methyl*-3-*indole*]-[4-*dimethylaminobenzene*]-β-*carbethoxy*-α-*methyltrimethincyanine* in yellow feathery needles, m. p. 141° (Found: C, 77·0; H, 7·1. $C_{24}H_{26}O_2N_2$ requires C, 77·0; H, 7·0%). It was yellow in ethanol, becoming intense blue with a trace of acid. 2-Methylindole (1·3 g.) and acetophenone (3 c.c.) were treated with concentrated sulphuric acid (0·6 c.c.) with shaking. After 20 mins., excess of acetophenone was removed in a high vacuum, and the residue heated with acetic acid (15 c.c.) and aldehyde (1·5 g.) for 1 hour on the steam-bath. [2-*Methyl*-3-*indole*]-[4-*dimethylaminobenzene*]-α-*phenyltrimethincyanine sulphate* was purified by repeated precipitation with ether from acetic acid; it had m. p. 211° (decomp.) and gave an intense blue solution in ethanol (Found: N, 6·1; S, 7·1. $C_{26}H_{26}O_4N_2S$ requires N, 6·3; S, 6·9%). 2-Phenylindole (2 g.) and acetone (5 c.c.) were treated dropwise at 0° with concentrated sulphuric acid (0·55 c.c.). Excess of acetone was decanted, and the oily product boiled for 30 mins. with acetic acid (10 c.c.) and aldehyde (1·5 g.). The green solution was poured into dilute ammonia and the precipitate taken up in chloroform and chromatographed on alumina. [2-*Phenyl*-3-*indole*]-[4-*dimethylaminobenzene*]-α-*methyltrimethincyanine* was crystallised several times from chloroform–light petroleum and then had m. p. 219° (Found: C, 85·5; H, 6·3; N, 7·5. $C_{26}H_{24}N_2$ requires C, 85·7; H, 6·6; N, 7·7%). It was yellow in ethanol, becoming green in presence of acid.

The authors thank Prof. I. M. Heilbron, D.S.O., F.R.S., for his interest and encouragement and Imperial Chemical Industries, Ltd., Dyestuffs Division, for gifts of chemicals.

Imperial College of Science and Technology, London, S.W.7. [*Received, April 24th*, 1944.]

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134. *Quinoxaline Cyanines. Part IV. Some Halogenated Styryl Derivatives.*

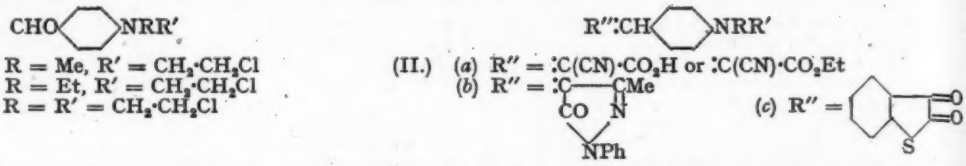
By R. M. Anker and A. H. Cook.

Three halogenated analogues of *p*-dimethylaminobenzaldehyde have been prepared and converted into styryl dyes by condensation with quaternary salts and other systems containing reactive methyl or methylene groups. Quinoxaline and hydroxyquinoxaline representatives recall the derivatives of dimethylaminobenzaldehyde in their intense blue colour.

In Parts I and II (J., 1942, 710; 1943, 394) of this series there is described the condensation of quinoxalines and hydroxyquinoxalines with *p*-dimethylaminobenzaldehyde. B.P. 456,534 describes the preparation of some *p*-chloroalkylaminobenzaldehydes, and their condensation with reactive methyl or methylene groups is mentioned in B.P. 458,405. The halogen atoms in the resulting condensation products were stated to improve the shade and dyeing properties, and in view of the potential interest of quinoxaline dyes previously described for application to textiles, the preparation of p-*methyl*-β-*chloroethyl*- (I*a*), p-*ethyl*-β-*chloroethyl*- (I*b*), and p-di-β-*chloroethyl*-*aminobenzaldehyde* (I*c*) was undertaken, and their condensation with typical quinoxaline quaternary salts studied. The opportunity was also taken to prepare for comparative purposes condensation products between these aldehydes and other typical cyanine components.

The aldehydes were obtaiued from methyl- or ethyl-aniline or aniline itself by introducing one or two *N*-hydroxyethyl groups; by using ethylene chlorohydrin in presence of magnesium oxide, formation of phenylmorpholine and other by-products was largely avoided. Chloroethylanilines resulted on treating the hydroxy-

ethyl derivatives with thionyl chloride, and the aldehyde groups were introduced with formomethylanilide and phosphorus oxychloride.



These aldehydes behaved like dimethylaminobenzaldehyde but were generally less reactive. For instance, condensation with cyanoacetic acid or ester in alcoholic solution with a basic catalyst gave yellow-orange dyes (II*a*), and red dyes (II*b*) were obtained by condensation with 1-phenyl-3-methyl-5-pyrazolone. Further, red-brown dyes (II*c*) were formed by reaction with thioindoxyls in boiling acetic anhydride solution. Condensation with quaternary salts of α-picoline, quinaldine, 2-methylbenzthiazole, 2 : 3 : 3-trimethylindolenine, and 2-methyl-3 : 4-dihydroquinazolone in acetic anhydride, or ethanol containing piperidine afforded the corresponding styryl dyes in good yields. With quaternary salts of 2 : 3-dimethylquinoxaline, however, reaction was often effected cleanly in chloroform or tetrachloroethane containing molecular quantities of pyridine and acetic anhydride; the use of mixtures of pyridine and acetic anhydride alone was disappointing, although it was very effective with dimethylaminobenzaldehyde (cf. Part I); it appeared that the present dyes were still less stable or less readily formed in such media than those described earlier. Finally, condensation with 2-methyl-3-keto-3 : 4-dihydroquinoxaline and its derivatives * after previous quaternisation with methyl sulphate was effected in acetic anhydride containing a little pyridine; more of the basic catalyst gave obviously different products which were only coloured in solution in mineral acid.

Most of the dyes so prepared were markedly less soluble in the common solvents than the similar dyes derived from *p*-dimethylaminobenzaldehyde; in particular, the methiodides of some of the phenyl-substituted quinoxaline derivatives had only a slight solubility in water. The strong bathochromic influence of the quinoxaline system was again well marked, but spectrometric comparison of representative quinoxaline dyes revealed no significant differences in the shape of the absorption curves or in the positions of the absorption maxima. There were irregular differences in the intensity of absorption but these were probably solvent effects and were insufficient to produce any considerable change of shade. It seems therefore that the strong bathochromic influence of the quinoxaline system masks the effect of the halogen atoms which appears in other dyes.

Experimental.

p-*Methyl-β-chloroethylaminobenzaldehyde.*—Methyl-β-hydroxyethylaniline (Laun, *Ber.*, 1884, **17**, 676) (200 g.) in benzene (200 c.c.) was treated gradually with phosphorus oxychloride (60 c.c.), reaction being completed on the steam-bath for 1 hour. The cold product was poured into water (500 c.c.), treated with a slight excess of sodium hydroxide, and the oil extracted with benzene. Distillation, eventually in a vacuum, gave methyl-β-chloroethylaniline as an oil, b. p. 130°/14 mm. (yield, 190 g.) (Found: Cl, 20·9. Calc. for $C_9H_{12}NCl$: Cl, 20·9%) (cf. Clemo and Perkin, J., 1922, **121**, 642). Phosphorus oxychloride (220 c.c.) was added to a mixture of formomethylanilide (320 g.) and benzene (100 c.c.); after being stirred for 1 hr., the mixture was kept at 0° during addition of methyl-β-chloroethylaniline (190 g.) diluted with an equal volume of benzene. Finally, after being heated at 30—35° for 4 hrs., the mixture was poured on ice, and the solution neutralised with sodium hydroxide. From the extract, benzene and methylaniline were removed in a rapid current of steam, and the remaining *aldehyde* (70 g.) recrystallised from methanol; it had m. p. 70° (Found: C, 60·9; H, 6·0; N, 7·1. $C_{10}H_{12}ONCl$ requires C, 60·7; H, 6·1; N, 7·1%).

p-*Ethyl-β-chloroethylaminobenzaldehyde.*—Ethyl-β-hydroxyethylaniline (180 g.; b. p. 151°/14 mm.) was treated as its homologue in the preceding preparation. Ethyl-β-chloroethylaniline (170 g.) was obtained as an oil, b. p. 133°/14 mm. The *aldehyde* (80 g.) was a very viscous liquid which did not solidify; it had b. p. 162°/0·02 mm., or 95° in a high vacuum, and could only be distilled without decomposition at low pressure (Found: N, 6·9. $C_{11}H_{14}ONCl$ requires N, 6·6%). The *semicarbazone* recrystallised from pyridine; m. p. 201° (Found: Cl, 13·0. $C_{12}H_{17}ON_4Cl$ requires Cl, 13·2%).

p-*Di-β-chloroethylaminobenzaldehyde.*—Aniline (1 g.-mol.) and ethylene chlorohydrin (1 g.-mol.), treated as in previous preparations (Knorr, *Ber.*, 1889, **22**, 2092), gave β-hydroxyethylaniline (0·9 g.-mol.), b. p. 185°/14 mm., which on further treatment with a molecular quantity of ethylene chlorohydrin gave di-β-hydroxyethylaniline (0·8 g.-mol.). The reaction could be carried out in one stage if its difficultly controllable nature and formation of " diethylene dianiline," m. p. 164°, were mitigated by stirring with 1 equiv. of magnesium oxide. Di-β-hydroxyethylaniline crystallised from benzene and had m. p. 59° (Found: C, 66·4; H, 8·3. Calc. for $C_{10}H_{15}O_2N$: C, 66·6; H, 8·4%). Di-β-chloroethylaniline was obtained in the usual way in almost theoretical yield; it distilled at 181°/14 mm. and, recrystallised from methanol, had m. p. 49°; Robinson and Watt (J., 1934, 1536) give m. p. 45° (Found: Cl, 32·6. Calc. for $C_{10}H_{13}NCl_2$: Cl, 32·6%). p-*Di-β-chloroethylaminobenzaldehyde* was prepared (yield, 70%) from the aniline in the usual manner. It crystallised from ethanol and had m. p. 88·5° (Found: N, 5·55; Cl, 28·2. $C_{11}H_{13}ONCl_2$ requires N, 5·7; Cl, 28·8%).

Condensations with Ethyl Cyanoacetate.—*p*-Methyl-β-chloroethylaminobenzaldehyde (7·7 g.) was boiled for 4 hrs. with ethanol (50 c.c.), ethyl cyanoacetate (5·0 g.), and piperidine (3 drops), and then cooled to 0°. *Ethyl* p-*methyl-β-chloroethylaminobenzylidenecyanoacetate* (11 g.) was filtered off, and recrystallised from ethanol, forming yellow microscopic needles, m. p. 105° (Found: N, 9·4. $C_{15}H_{17}O_2N_2Cl$ requires N, 9·5%). *Ethyl* p-*ethyl-β-chloroethylaminobenzylidenecyanoacetate* was prepared in the same way; it formed a yellow microcrystalline deposit, m. p. 124°, from ethanol (Found: N, 8·9. $C_{16}H_{19}O_2N_2Cl$ requires N, 9·1%).

Condensations with 1-*Phenyl*-3-*methyl*-5-*pyrazolone.*—The pyrazolone (5 g.) was refluxed with *p*-methyl-β-chloroethylaminobenzaldehyde (5·7 g.), ethanol (50 c.c.), and 3 drops of piperidine for 4 hrs. 1-*Phenyl*-3-*methyl*-4-p-*methyl-β-chloroethylaminobenzylidene*-5-*pyrazolone* separated on cooling; it crystallised from acetic acid in red needles, m. p. 154° (Found: N, 12·0. $C_{20}H_{20}ON_3Cl$ requires N, 11·9%). The 4-p-*ethyl* compound, prepared in the same way, formed

* Patent application pending.

red needles, m. p. 117°, from acetic acid (Found: N, 11·5. $C_{21}H_{22}ON_3Cl$ requires N, 11·4%); and the 4-p-*di-β-chloroethylamino*-analogue, similarly obtained from *p*-di-β-chloroethylaminobenzaldehyde (7·1 g.) and the pyrazolone (5 g.), formed red needles, m. p. 167°, from acetic acid (Found: N, 10·5. $C_{22}H_{21}ON_3Cl_2$ requires N, 10·45%).

Condensations with Indoxyls.—6-Ethoxythioindoxyl (3 g.) and *p*-methyl-β-chloroethylaminobenzaldehyde (3 g.) were dissolved in ethanol (50 c.c.) with concentrated hydrochloric acid (3 c.c.), and the solution refluxed for 1 hr. After cooling, the reddish-brown crystals were recrystallised from benzene or acetic acid. 6-*Ethoxy*-2-p-*methyl-β-chloroethylaminobenzylidenethioindoxyl* had m. p. 152° (yield, 3·5 g.) (Found: N, 3·5; Cl, 9·9. $C_{20}H_{20}O_2NSCl$ requires N, 3·5; Cl, 9·5%). 6-Chloro-4-methylthioindoxyl (4 g.) and *p*-di-β-chloroethylaminobenzaldehyde (5 g.) were refluxed for 1 hr. with acetic anhydride (50 c.c.); on cooling 6-*chloro*-4-*methyl*-2-p-*di-β-chloroethylaminobenzylidenethioindoxyl* (5·2 g.) separated; it was filtered off, washed with acetic acid, and recrystallised from anisole, forming red prisms, m. p. 191° (Found: N, 3·3; Cl, 24·3. $C_{20}H_{18}ONCl_3S$ requires N, 3·3; Cl, 25·0%).

Condensations with α-Picoline Ethiodide.—*p*-Ethyl-β-chloroethylaminobenzaldehyde (7 g.) was refluxed in ethanol (50 c.c.) with α-picoline ethiodide (7 g.) and piperidine (3 drops) for 4 hrs. 2-p-*Ethyl-β-chloroethylaminostyrylpyridine ethiodide* (8 g.) crystallised on cooling, and was recrystallised from ethanol; it formed red needles, m. p. 154° (Found: N, 6·55. $C_{19}H_{24}N_2ClI$ requires N, 6·35. 0·1795 G. gave 0·1533 g. of mixed silver halides. $C_{19}H_{24}N_2ClI$ requires 0·1560 g.). *p*-Di-β-chloroethylaminobenzaldehyde (8 g.), α-picoline ethiodide (8 g.), piperidine (2 c.c.), and ethanol (50 c.c.) were refluxed for 3½ hrs., and so much dye had then crystallised that boiling was discontinued. The main product, 2-p-*di-β-chloroethylaminostyrylpyridine ethiodide* (12 g.), was sparingly soluble in ethanol and was recrystallised from acetic acid; it formed a red solid, m. p. 191° (decomp.) (Found: N, 5·9. $C_{19}H_{23}N_2Cl_2I$ requires N, 5·9%. 0·1550 G. gave 0·1702 g. of mixed silver halides. $C_{19}H_{23}N_2Cl_2I$ requires 0·1697 g.). It was accompanied by 0·5 g. of a water-soluble, yellow powder which became red on boiling with ethanol; m. p. 300° (decomp.) (Found: N, 5·45%).

p-*Ethyl-β-chloroethylaminostyrylquinoline Methiodide.*—Quinaldine methiodide (5 g.) and *p*-ethyl-β-chloroethylaminobenzaldehyde (5 g.) were boiled for 5 mins. with acetic anhydride (50 c.c.), the solution cooled, and then poured into water (500 c.c.). On recrystallisation from ethanol, the dye was obtained in dark violet crystals, m. p. 191° (Found: N, 5·85. $C_{22}H_{24}N_2ClI$ requires N, 5·85%). Light absorption (ethanol): max. 5080 A.

Condensations with 2-Methylbenzthiazole Methiodide.—The methiodide (6 g.) and *p*-methyl-β-chloroethylaminobenzaldehyde (4 g.) were refluxed for 1 hr. in acetic anhydride (75 c.c.). The cooled solution was poured into water (700 c.c.), and the dye (6 g.) allowed to crystallise at 0°; 2-p-*methyl-β-chloroethylaminostyrylbenzthiazole methiodide* separated from ethanol in dark red prisms with a green lustre, m. p. 138° (Found: N, 6·0. $C_{19}H_{20}N_2SClI$ requires N, 5·95%). Light absorption (ethanol): max. 5020 A. 2-Methylbenzthiazole methiodide (3 g.) and *p*-ethyl-β-chloroethylaminobenzaldehyde (2·1 g.) were refluxed for 4 hrs. with ethanol (30 c.c.) containing piperidine (3 drops). The warm solution was poured into 10% aqueous sodium iodide (300 c.c.), the whole cooled to 0° overnight, and the dye collected. 2-p-*Ethyl-β-chloroethylaminostyrylbenzthiazole methiodide*, after several crystallisations from ethanol, formed brownish-red needles (3 g.), m. p. 198° (decomp.) (Found: N, 5·5. $C_{20}H_{22}N_2SClI$ requires N, 5·8%. 0·1431 G. gave 0·1134 g. of mixed halides. $C_{20}H_{22}N_2SClI$ requires 0·1153 g.).

Condensations with 2 : 3 : 3-Trimethylindolenine Methiodide.—The iodide (3 g.) and *p*-methyl-β-chloroethylaminobenzaldehyde (2 g.) were refluxed in ethanol (30 c.c.) containing piperidine (3 drops) for 4 hrs., and the dark red solution poured into 10% sodium iodide solution (300 c.c.). After keeping at 0°, the dye was washed with ether and then with water, and finally crystallised several times from 60% ethanol. 2-p-*Methyl-β-chloroethylaminostyryl*-3 : 3-*dimethylindolenine methiodide* (2 g.) formed red needles with a green sheen, m. p. 148° (Found: N, 5·6. $C_{23}H_{26}N_2ClI$ requires N, 5·8%. 0·1429 G. gave 0·1095 g. of mixed silver halides. $C_{23}H_{26}N_2ClI$ requires 0·1124 g.). The indolenine methiodide (4·5 g.) was condensed for 4 hrs. with *p*-di-β-chloroethylaminobenzaldehyde (3 g.) in boiling ethanol (40 c.c.) and piperidine (3 drops). The crude dye was salted out with 400 c.c. of 10% sodium iodide, dissolved in chloroform, and the solution filtered and precipitated with 10 vols. of ether. 2-p-*Di-β-chloroethylaminostyryl*-3 : 3-*dimethylindolenine methiodide* recrystallised from 70% ethanol in red needles with a green lustre, m. p. 127° (Found: N, 5·0. $C_{23}H_{27}N_2Cl_2I$ requires N, 5·3%. 0·1129 G. gave 0·1119 g. of mixed silver halides. $C_{23}H_{27}N_2Cl_2I$ requires 0·1116 g.).

2-Methyl-3 : 4-dihydroquinazolone methiodide (3·6 g.) and *p*-methyl-β-chloroethylaminobenzaldehyde (2·5 g.) were heated to 145—150° in acetic anhydride (80 c.c.) for 20 mins. The deep brown solution was cooled, and the product (1·9 g.) recrystallised from formic acid. 2-p-*Methyl-β-chloroethylaminostyryl*-3 : 4-*dihydroquinazolone methiodide* formed brick-red crystals, m. p. 220° (decomp.) (Found: N, 8·5. $C_{20}H_{21}ONClI$ requires N, 8·7%. 0·1106 G. gave 0·0878 g. of mixed silver halides. $C_{20}H_{21}ONClI$ requires 0·0870 g.).

Condensations with Quinoxalines.—2-Aminodiphenylamine (9·2 g.) in ethanol (40 c.c.) was treated slowly with diacetyl (4·3 g.) with cooling and stirring. After 5 mins., hydriodic acid (13 g., *d* 1·7) was slowly added, and the crystalline 1-*phenyl*-2 : 3-*dimethylquinoxalinium iodide* (9 g.) collected and repeatedly crystallised from 90% ethanol; m. p. 204° (decomp.) (Found: N, 7·5; I, 35·5. $C_{16}H_{15}N_2I$ requires N, 7·7; I, 35·1%). When this iodide (1·9 g.) was heated in acetic anhydride (10 c.c.) at 100° for 10 mins. with *p*-methyl-β-chloroethylaminobenzaldehyde (1 g.), and the cooled solution poured into ether (100 c.c.), 1-*phenyl*-2-p-*methyl-β-chloroethylaminostyryl*-3-*methylquinoxalinium iodide* was formed; it was dissolved in ethanol, salted out with aqueous sodium iodide, and finally recrystallised from ethanol (yield, 0·6 g.); m. p. 150° (Found: N, 7·5. $C_{26}H_{25}N_2ClI$ requires N, 7·7%. 0·1818 G. gave 0·1287 g. of mixed silver halides. $C_{26}H_{25}N_2ClI$ requires 0·1271 g.). Light absorption (ethanol): max. *ca.* 6250 A. 1-Phenyl-2 : 3-dimethylquinoxalinium iodide (3 g.) was condensed with *p*-ethyl-β-chloroethylaminobenzaldehyde (2 g.) in tetrachloroethane (30 c.c.) containing acetic anhydride (2 c.c.) and pyridine (1 c.c.) at 100° for 15 mins. The product was poured into ether (300 c.c.), the dye filtered off, dissolved in ethanol, and salted out with excess of aqueous potassium iodide (yield, 3·5 g.). 1-*Phenyl*-2-p-*ethyl-β-chloroethylaminostyryl*-3-*methylquinoxalinium iodide*, recrystallised from ethanol, had m. p. 170° (Found: C, 58·1; H, 5·0. $C_{27}H_{27}N_2ClI$ requires C, 58·3; H, 4·9%. 0·1670 G. gave 0·1105 g. of mixed silver halides. $C_{27}H_{27}N_2ClI$ requires 0·1137 g.). By replacing the phenyl iodide by 2 : 3-dimethylquinoxaline methiodide in the preceding preparation, 2-p-*ethyl-β-chloroethylaminostyryl*-3-*methylquinoxaline methiodide* was obtained; it separated from ethanol in needles, m. p. 130° (Found: C, 53·6; H, 5·4. $C_{22}H_{24}N_2ClI$ requires C, 53·5; H, 5·1%. 0·1251 G. gave 0·0955 g. of mixed silver halides. $C_{22}H_{24}N_2ClI$ requires 0·0986 g.). 2-p-*Methyl-β-chloroethylaminostyryl*-3-*methylquinoxaline methiodide* was prepared similarly; it separated from ethanol and had m. p. 135° (Found: C, 52·6; H, 5·3. $C_{21}H_{22}N_2ClI$ requires C, 52·6; H, 4·8%. 0·1466 G. gave 0·1092 g. of mixed silver halides. $C_{21}H_{22}N_2ClI$ requires 0·1119 g.). Light absorption (ethanol): max. 6200 A.

Condensations with 2-Methyl-3 : 4-dihydro-3-quinoxalone.—The quinoxalone (4 g.) was heated with methyl sulphate (9 g.) for 10 mins. at 140°, the product cooled, and excess of methyl sulphate removed by washing with ether. To the residue, acetic anhydride (30 c.c.) was added, followed by *p*-methyl-β-chloroethylaminobenzaldehyde (5 g.) and pyridine (1 c.c.). The solution was heated to boiling, cooled, and the dye precipitated with ether (300 c.c.). The solid was taken up in ethanol, salted out by pouring into 10 vols. of aqueous 10% sodium iodide solution, and the resulting dye (8·5 g.) crystallised from 60% formic acid, affording fine green needles. 2-p-*Methyl-β-chloroethylaminostyryl*-3 : 4-*dihydro*-3-*quinoxalone methiodide* had m. p. 214° (decomp.) and gave intensely blue solutions (Found: C, 49·4; H, 4·2.

$C_{29}H_{21}N_3ClI$ requires C, 49·8; H, 4·4%. 0·1378 G. gave 0·1099 g. of mixed silver halides. $C_{29}H_{21}N_3ClI$ requires 0·1083 g.). Light absorption (ethanol): max. 5900 A. The quinoxalone (7 g.) was made into a paste with methyl sulphate (15 g.) and heated for 10 mins. at 140°. The product was dissolved in acetic anhydride (30 c.c.), treated with di-β-chloroethylaminobenzaldehyde (10 g.) in the same solvent (30 c.c.), and the whole boiled for 15 mins. The solution was cooled, poured into water (600 c.c.), and the solid extracted with boiling acetic acid; the undissolved residue had no dyeing properties, and the crystalline deposit (2·5 g.) from the acetic acid contained two constituents separated by fractional crystallisation from ethanol. The less soluble 2-p-*di-β-chloroethylaminostyryl*-3 : 4-*dihydro*-3-*quinoxalone methosulphate* separated as a dark blue, microcrystalline powder with a green lustre, m. p. 198° (Found: N, 8·05; Cl, 14·2. $C_{32}H_{35}O_5N_3Cl_2S$ requires N, 8·15; Cl, 13·8%). Light absorption (ethanol): max. 6000 A. The second constituent, possibly the *dimethosulphate* of the same cyanine base, separated in blue needles, m. p. 146° (Found: N, 6·3, 6·4. $C_{34}H_{31}O_9N_3S_2Cl_2$ requires N, 6·55%).

Condensations with 2 : 4-*Dimethyl*-3 : 4-*dihydro*-3-*quinoxalone*.—The quinoxalone (1·8 g.) was quaternised with methyl sulphate (1·3 g.) at 140° for 10 mins., the product dissolved in acetic anhydride (10 c.c.), and a solution of *p*-methyl-β-chloroethylaminobenzaldehyde (2 g.) in the same solvent (10 c.c.) added. The whole was boiled under reflux for 5 mins., cooled, and poured into 10% aqueous sodium iodide (200 c.c.). 2-p-*Methyl-β-chloroethylaminostyryl*-4-*methyl*-3 : 4-*dihydro*-3-*quinoxalone methiodide* (2 g.) was filtered off and crystallised from ethanol; it had m. p. 161° (Found: N, 8·7. $C_{21}H_{22}ON_3ClI$ requires N, 8·5%. 0·1466 G. gave 0·1092 g. of silver halides. $C_{21}H_{22}ON_3ClI$ requires 0·1119 g.). Light absorption (ethanol): max. 6170 A. The quinoxalone (8 g.) was quaternised with methyl sulphate (6 g.) as above, the product dissolved in acetic anhydride (40 c.c.), and *p*-di-β-chloroethylaminobenzaldehyde (12 g.) in pyridine (20 c.c.) added. The whole was boiled for 5 mins., poured into water (400 c.c.), and the dye salted out with sodium chloride; it was crystallised from acetic acid, or from ethanol in which it was less soluble; 2-*di-β-chloroethylaminostyryl*-4-*methyl*-3 : 4-*dihydroquinoxalone methochloride* had m. p. 192° (decomp.) (Found: N, 9·5; Cl, 23·4. $C_{22}H_{24}ON_3Cl_3$ requires N, 9·3; Cl, 23·6%). Light absorption (ethanol): max. 5750 A.

Condensations with 4-*Phenyl*-2-*methyl*-3 : 4-*dihydro*-3-*quinoxalone*.—Methyl sulphate (2·5 g.) and the quinoxalone (5 g.) were heated to 140° for 20 mins., the product taken up in acetic anhydride (30 c.c.), a solution of *p*-methyl-β-chloroethylaminobenzaldehyde (4·5 g.) in acetic anhydride (10 c.c.) added, and the whole heated under reflux for 15 mins.; the mixture was then poured into water (400 c.c.), and the solid was filtered off. 4-*Phenyl*-2-p-*methyl-β-chloroethylaminostyryl*-3 : 4-*dihydro*-3-*quinoxalone methosulphate* crystallised from ethanol and had m. p. 189° (decomp.) (Found: Cl, 6·65. $C_{27}H_{28}O_5N_3SCl$ requires Cl, 6·55%). Light absorption (ethanol): max. 6200 A. 4-*Phenyl*-2-p-*di-β-chloroethylaminostyryl*-3 : 4-*dihydro*-3-*quinoxalone methosulphate*, prepared similarly, crystallised from ethanol and had m. p. 170° (decomp.) (Found: N, 7·4; Cl, 12·3. $C_{28}H_{29}O_5N_3Cl_2S$ requires N, 7·1; Cl, 12·0%). Light absorption (ethanol): max. 6000 A.

The authors thank I.C.I. (Dyestuffs) Ltd. for grants and gifts of chemicals, and Professor I. M. Heilbron, F.R.S., for his constant encouragement and advice.

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135. *Sugar Nitrates. Part I. Syntheses of* 2 : 4-*Dimethyl* β-*Methylglucoside and* 2 : 4 : 6-*Trimethyl* β-*Methylglucoside.*

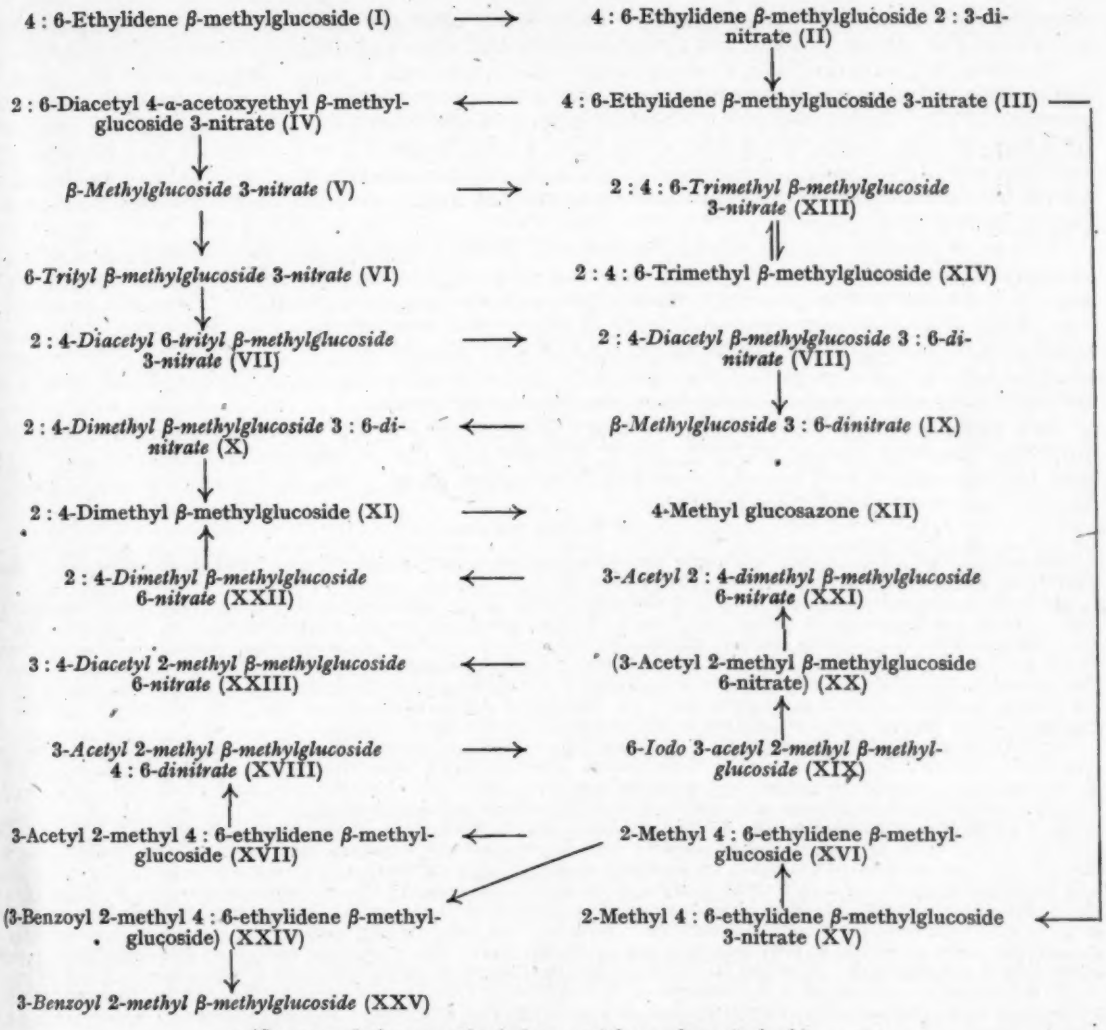
By JOHN DEWAR and GODFREY FORT.

Two syntheses of 2 : 4-dimethyl β-methylglucoside and one of 2 : 4 : 6-trimethyl β-methylglucoside, all originating from 4 : 6-ethylidene β-methylglucoside 2 : 3-dinitrate, are described: these illustrate the uses of nitration and denitration and allied processes in this field. Details are given of a number of new derivatives, mainly nitrates, of β-methylglucoside.

THE experiments recorded here and in the following two papers were undertaken with a view to complete the series of partly methylated glucopyranoses, of which the 2 : 4-dimethyl and the 3 : 4-dimethyl derivative were unknown; subsequently, two syntheses of 2 : 4-dimethyl β-methylglucoside were described by Reeves, Adam, and Goebel (*J. Biol. Chem.*, 1941, **140**, 653), who also showed that the dimethyl methylglucoside isolated by Robertson and Waters (J., 1931, 1707) was, in fact, 2 : 4-dimethyl α-methylglucoside.

The nitration of 4 : 6-benzylidene β-methylglucoside was found by Oldham (*J. Soc. Chem. Ind.*, 1934, **53**, 236T) to promote the simultaneous formation of a nitrobenzylidene substituent in addition to the introduction of nitrate groups into positions 2 and 3, and this nitrobenzylidene residue could not subsequently be removed by normal hydrolysis processes. Use of 4 : 6-ethylidene β-methylglucoside (Helferich and Appel, *Ber.*, 1931, **64**, 1841) in place of the corresponding benzylidene compound avoided the complication of substituent nitration, and Oldham was able to remove preferentially one of the two nitrate groups. Later, one of us (J. D.), in collaboration with Oldham (unpublished result), repeated this work and showed that the dinitrate on treatment with sodium iodide in acetone (cf. Bell and Synge, J., 1937, 1711; 1938, 833) gave 4 : 6-ethylidene β-methylglucoside 3-nitrate. From this compound various routes towards 2 : 4-dimethyl β-methylglucoside suggested themselves: two of these were completed, and a number of intermediate and subsidiary compounds (mainly nitrates) of value for reference purposes were isolated and characterised. The various steps are shown in the table.

Modification of the processes described by Helferich and Appel (*loc. cit.*) and by Appel and Haworth (J., 1938, 793) gave almost quantitative conversion of β-methylglucoside into 4 : 6-ethylidene β-methylglucoside (I), which, under the conditions employed by us, was largely formed in preference to the subsidiary product 2 : 3-oxidodiethylidene 4 : 6-ethylidene β-methylglucoside. Nitration of (I) gave rise to different products according to the method adopted: in the normal process, using a mixture of chloroform and fuming nitric acid at 0° (cf. Oldham, J., 1925, **127**, 2840, *et seq.*), removal of the ethylidene residue took place as well as


4 : 6-Ethylidene β-methylglucoside (I)
4 : 6-Ethylidene β-methylglucoside 2 : 3-dinitrate (II)
4 : 6-Ethylidene β-methylglucoside 3-nitrate (III)
2 : 6-Diacetyl 4-α-acetoxyethyl β-methylglucoside 3-nitrate (IV)
β-Methylglucoside 3-nitrate (V)
2 : 4 : 6-Trimethyl β-methylglucoside 3-nitrate (XIII)
2 : 4 : 6-Trimethyl β-methylglucoside (XIV)
6-Trityl β-methylglucoside 3-nitrate (VI)
2 : 4-Diacetyl 6-trityl β-methylglucoside 3-nitrate (VII)
2 : 4-Diacetyl β-methylglucoside 3 : 6-dinitrate (VIII)
β-Methylglucoside 3 : 6-dinitrate (IX)
2 : 4-Dimethyl β-methylglucoside 3 : 6-dinitrate (X)
2 : 4-Dimethyl β-methylglucoside (XI)
4-Methyl glucosazone (XII)
2 : 4-Dimethyl β-methylglucoside 6-nitrate (XXII)
3-Acetyl 2 : 4-dimethyl β-methylglucoside 6-nitrate (XXI)
3 : 4-Diacetyl 2-methyl β-methylglucoside 6-nitrate (XXIII)
(3-Acetyl 2-methyl β-methylglucoside 6-nitrate) (XX)
3-Acetyl 2-methyl β-methylglucoside 4 : 6-dinitrate (XVIII)
6-Iodo 3-acetyl 2-methyl β-methylglucoside (XIX)
3-Acetyl 2-methyl 4 : 6-ethylidene β-methylglucoside (XVII)
2-Methyl 4 : 6-ethylidene β-methylglucoside (XVI)
(3-Benzoyl 2-methyl 4 : 6-ethylidene β-methylglucoside) (XXIV)
2-Methyl 4 : 6-ethylidene β-methylglucoside 3-nitrate (XV)
3-Benzoyl 2-methyl β-methylglucoside (XXV)

(Compounds in parenthesis have not been characterised.)

the introduction of nitrate groups, the product being β-methylglucoside 2 : 3 : 4 : 6-tetranitrate (Part III), whereas application of the alternative method developed by Oldham (cf. Bell and Synge, *loc. cit.*), in which a non-acidic solution of dinitrogen pentoxide in chloroform is used, produced no substantial removal of the ethylidene group.

For the removal of the 2-nitrate group from (II), Bell and Synge (*loc. cit.*) advocate a period of heating with sodium iodide and acetone of only 1 hour, but we found that a period of about 20 hours was necessary, preferably with cooling and release of pressure after 10 hours. By these means we were able to obtain consistently pure 4 : 6-ethylidene β-methylglucoside 3-nitrate (III) in 40% of the theoretical amount. Removal of the ethylidene residue to give (IV), followed by alkaline hydrolysis [cf. Gladding and Purves, *J. Amer. Chem. Soc.*, 1944, **66**, 76, 153), gave β-*methylglucoside* 3-*nitrate* (V), the structure of which was further confirmed by methylation to 2 : 4 : 6-*trimethyl* β-*methylglucoside* 3-*nitrate* (XIII), which, on removal of the nitrate group, gave the known 2 : 4 : 6-trimethyl β-methylglucoside (XIV) (Oldham, *J. Amer. Chem. Soc.*, 1934, **56**, 1360; Freudenberg and Plankenhorn, *Annalen*, 1938, **536**, 257; Lake and Peat, J., 1938, 1417). Incidentally, these processes provide a convenient method for the preparation of 2 : 4 : 6-trimethyl β-methylglucoside.

The mononitrate (V) condensed readily with trityl chloride in anhydrous pyridine to give the 6-*trityl* compound (VI), which, though itself non-crystalline, gave crystalline 2 : 4-*diacetyl* 6-*trityl* β-*methylglucoside* 3-*nitrate* (VII). Treatment with fuming nitric acid in chloroform gave a mixture of 2 : 4-*diacetyl* β-*methylglucoside* 3 : 6-*dinitrate* (VIII) and tritylcarbinol: separation of the constituents was not attempted at this stage, but after deacetylation by the Zemplen method crystalline β-*methylglucoside* 3 : 6-*dinitrate* (IX) was obtained by extraction of the carbinol with benzene from aqueous solution. Methylation readily gave 2 : 4-*dimethyl* β-*methylglucoside* 3 : 6-*dinitrate* (X), from which the nitrate residues were removed, giving

crystalline 2 : 4-dimethyl β-methylglucoside (XI). This substance had characteristics in agreement with those quoted by Adams, Reeves, and Goebel (*loc. cit.*), and, after hydrolysis, gave 4-methylglucosazone.

In the second main synthesis, 4 : 6-ethylidene β-methylglucoside 3-nitrate was converted into the 2-methyl compound (XV) from which the nitrate group could be removed to give 2-methyl 4 : 6-ethylidene β-methylglucoside (XVI). Acetylation gave 3-acetyl 2-methyl 4 : 6-ethylidene β-methylglucoside (XVII), and from this, by treatment with fuming nitric acid in the cold, 3-*acetyl* 2-*methyl* β-*methylglucoside* 4 : 6-*dinitrate* (XVIII) was obtained in good yield. Denitration of this with simultaneous introduction of iodine into the 6-position (cf. Oldham and Rutherford, *J. Amer. Chem. Soc.*, 1932, **54**, 366) gave 6-*iodo* 3-*acetyl* 2-*methyl* β-*methylglucoside* (XIX), again in good yield.

It seemed possible that the presence of iodine in position 6 might lead to complications if methylation were attempted by Purdie's method, and therefore the corresponding 6-nitrate (XX) was prepared; this was non-crystalline but readily gave rise to the crystalline *diacetyl* derivative (XXIII). Conversion by methylation into (XXI) and subsequent deacetylation to (XXII) gave a syrup in each case, but in the final stage, the removal by reduction of the nitrate group from (XXII), a good yield of 2 : 4-dimethyl β-methylglucoside, identical with the previous product, was obtained. The intermediate syrups (XXI) and (XXII) were probably not pure, some acyl migration having taken place during methylation.

In a subsidiary experiment, (XVI) was benzoylated, giving a syrup, essentially 3-benzoyl 2-methyl 4 : 6-ethylidene β-methylglucoside (XXIV), and it is noteworthy that subsequent treatment of this derivative with 1% hydrochloric acid served to remove the ethylidene group, giving a crystalline product, presumably 3-*benzoyl* 2-*methyl* β-*methylglucoside* (XXV).

Experimental.

All evaporations were carried out under diminished pressure and, unless otherwise stated, at below 50°. The light petroleum used in recrystallisations was of b. p. 60—80°.

4 : 6-*Ethylidene β-Methylglucoside* (I).—β-Methylglucoside (50 g.), paraldehyde (180 c.c.; dried over calcium chloride), concentrated sulphuric acid (0·44 c.c.), and some 20 small glass beads were shaken together for 48 hours, after which the solid portion (30 g.) of the reaction mixture was filtered off, washed twice with light petroleum, and recrystallised twice from methylated spirit, giving 4 : 6-ethylidene β-methylglucoside (m. p. 185—186°) pure enough for nitration. The paraldehyde filtrate gave 2 : 3-oxidodiethylidene 4 : 6-ethylidene β-methylglucoside (1—2 g.), which was converted into more 4 : 6-ethylidene β-methylglucoside by Appel and Haworth's method (*loc. cit.*). Utilisation of recovered materials in subsequent preparations made the conversion almost quantitative.

4 : 6-*Ethylidene β-Methylglucoside* 2 : 3-*Dinitrate* (II).—This was prepared by Oldham's method (unpublished result) [compare Bell and Synge (*loc. cit.*)]. Good yields (average 75%) were obtained by using not more than 3 g. of 4 : 6-ethylidene β-methylglucoside; on a larger scale the yield was considerably diminished. In practice, 8—10 samples were nitrated separately, and the combined chloroform extracts purified.

4 : 6-*Ethylidene β-Methylglucoside* 3-*Nitrate* (III).—The dinitrate (II) (10 g.), sodium iodide (20 g.), and acetone (70 c.c.) were heated in a sealed tube (capillary end) for 10 hours in a boiling water-bath. After cooling (overnight), the internal gas pressure was released by carefully fusing the fine capillary end with a small flame, the tube resealed, and heating continued for a further 10 hours. After cooling (overnight), the solvent was removed by distillation, and the residue shaken with chloroform and water. The chloroform layer was shaken in turn with sodium thiosulphate solution and with potassium hydrogen carbonate solution, and, after drying with sodium sulphate and simultaneously decolorising with norit, the solvent was removed by distillation. The crystalline residue was recrystallised from ethyl alcohol–light petroleum (2 : 1), giving (III) (8·6 g.) fine needles, m. p. 147°, $[\alpha]_D^{18°}$ −31·1° (chloroform, $l = 2$, $c = 1·6$).

2 : 6-*Diacetyl* 4-α-*Acetoxyethyl β-Methylglucoside* 3-*Nitrate* (IV).—The compound (III) (10 g.), on treatment with acetic anhydride (300 c.c.) and sulphuric acid (0·2 c.c.) (cf. Bell and Synge, *loc. cit.*), yielded a syrup (14·4 g.) from which crystals (6·3 g.), m. p. 125—126°, were obtained (*ex* ethyl alcohol and light petroleum).

β-Methylglucoside 3-*Nitrate* (V).—Methyl alcohol (62 c.c.) containing sodium methoxide (0·075 g. of sodium) was added to a solution of (IV) (6·2 g.) in chloroform (62 c.c.), and the course of the reaction followed polarimetrically, a constant value [$\alpha_D = -1·77°$ ($l = 2$)] being reached in 20 mins. Glacial acetic acid (0·184 c.c.) was then added, the solvent removed by distillation, the residue extracted with acetone, and the solvent distilled from this extract. A solution of the resultant glass (3·8 g.) in water was shaken thrice with chloroform, and subsequent evaporation of the aqueous solution gave a residue, from which by extraction with acetone and subsequent evaporation was obtained a glass (3·6 g.). Recrystallisation from water gave the product, m. p. 104—108°, $[\alpha]_D^{13°}$ −16·8° (ethyl alcohol, $l = 2$, $c = 5·222$) (Found: C, 35·0; H, 5·6; N, 6·0; OMe, 12·9. $C_7H_{13}O_8N$ requires C, 35·1; H, 5·4; N, 5·9; OMe, 13·0%).

6-*Trityl β-Methylglucoside* 3-*Nitrate* (VI).—The compound (V) (3·5 g.) and trityl chloride (3·93 g.) in dry pyridine (15 c.c.) were heated for 1 hour in a stoppered flask at 100° and thereafter poured into water (300 c.c.); the resulting gum was dissolved in benzene, and washed with 2% sulphuric acid, then 2% sodium hydroxide, and finally water. After drying (sodium sulphate), the solvent was distilled off, giving a glass in quantitative yield (Found: OMe, 5·7. $C_{26}H_{27}O_8N$ requires OMe, 6·4%). For the characterisation of the compound, purer material was obtained from the deacetylation of (VIII) (below); a solution of this compound (0·967 g.) in chloroform (15 c.c.) was treated in the cold with methyl alcohol in which sodium (9 mg.) had been dissolved. The progress of the reaction was followed polarimetrically, and after 40 hours the calculated amount of glacial acetic acid (0·022 c.c.) was added, and the solvent distilled off. The residue was treated with chloroform and the resulting solution washed with potassium hydrogen carbonate solution. The chloroform solution was dried (sodium sulphate), and removal of the solvent gave a colourless glass (0·832 g.) which softened at about 65° and showed $[\alpha]_D^{13°}$ −22·3° (chloroform, $l = 2$, $c = 3·612$) (Found: C, 64·6; H, 5·6; N, 2·9; OMe, 6·1. $C_{26}H_{27}O_8N$ requires C, 64·9; H, 5·6; N, 2·9; OMe, 6·4%).

2 : 4-*Diacetyl* 6-*Trityl β-Methylglucoside* 3-*Nitrate* (VII).—Acetylation in the usual manner of a sample of (VI) (2·469 g.), obtained from (V) as above, yielded 2·479 g. of crystals, which were recrystallised from ethyl alcohol. The pure *nitrate* (needles) had m. p. 161—162°, $[\alpha]_D^{15°}$ +23·9° (chloroform, $l = 2$, $c = 4·203$) (Found: C, 63·8; H, 5·4; N, 2·5; OMe, 5·4. $C_{30}H_{31}O_{10}N$ requires C, 63·7; H, 5·5; N, 2·5; OMe, 5·5%).

2 : 4-*Diacetyl β-Methylglucoside* 3 : 6-*Dinitrate* (VIII).—The compound (VII) (2 g.), dissolved in chloroform (20 c.c.), was cooled in ice, and a cold solution of fuming nitric acid (20 c.c.) in chloroform (20 c.c.) added. After 10 minutes at 0° the reaction was arrested by shaking quickly with ice and water, and then with a dilute solution of potassium hydrogen carbonate. After drying (sodium sulphate), the solvent was distilled off, giving a glass (2·27 g.) comprising (VIII) admixed with a small amount of tritylcarbinol. Separation of these constituents proved difficult at this stage.

and, a more effective separation being possible after deacetylation (see below), the impure material was used for the next stage. The pure *compound* [m. p. 78—79° (*ex* ethyl alcohol); $[\alpha]_D^{17°}$ −16·3° (chloroform, $l = 1$, $c = 2·14$)] was obtained by acetylation of (IX) (below) (Found: C, 36·3; H, 4·6; OMe, 8·1. $C_{11}H_{16}O_{12}N_2$ requires C, 35·9; H, 4·4; OMe, 8·4%).

β-Methylglucoside 3 : 6-*Dinitrate* (IX).—The dinitrate (VIII) (4·5 g.) in chloroform (45 c.c.) was treated with methyl alcohol containing sodium methoxide (0·036 g. of sodium) at room temperature for 5½ hours, the rotation then having become constant. Glacial acetic acid (0·094 c.c.) was added, and the solution evaporated to dryness. The crude product was extracted from this residue with chloroform–acetone, and, after removal of these solvents by distillation, was dissolved in water. From the aqueous solution the admixed tritylcarbinol was removed by three extractions with benzene, and the water thereafter distilled off. The crystalline residue was extracted with acetone, and, after decolorising (norit), the solvent was distilled off, giving a colourless crystalline product (1·816 g.). Recrystallisation from chloroform gave needles, m. p. 144—145°, $[\alpha]_D^{14°}$ −7·8° (acetone, $l = 2$, $c = 3·8$) (Found: C, 30·2; H, 4·3; OMe, 11·0. $C_7H_{12}O_{10}N_2$ requires C, 29·6; H, 4·2; OMe, 10·9%).

2 : 4-*Dimethyl β-Methylglucoside* 3 : 6-*Dinitrate* (X).—After two treatments with methyl iodide and silver oxide the above substance (IX) (0·757 g.) gave a clear syrup (0·831 g.), $n_D^{13°}$ 1·4645, $[\alpha]_D^{13°}$ −7·1° (chloroform, $l = 2$, $c = 4·2$) (Found: N, 9·4; OMe, 29·8. $C_9H_{16}O_{10}N_2$ requires N, 9·0; OMe, 29·8%).

2 : 4-*Dimethyl β-Methylglucoside* (XI).—(*a*) The *dinitrate* (X) (0·536 g.) in glacial acetic acid (6 c.c.) was treated with an excess of a mixture of zinc and iron powder with gentle heat until a test drop gave no blue coloration with diphenylbenzidine in sulphuric acid. Isolation was effected by filtration (the residues being washed with chloroform), adding the filtrate to a concentrated solution of potassium carbonate, extracting the aqueous mixture 12 times with chloroform, drying (sodium sulphate), and decolorising (norit) the chloroform solution and distilling off the solvent. The crystalline product (0·408 g.) gave fine needles from light petroleum–ethyl alcohol; m. p. 124—125°, $[\alpha]_D^{14°}$ −16·3° (acetone, $l = 2$, $c = 3·074$), $[\alpha]_D^{15°}$ −22·1° (ethyl alcohol, $l = 2$, $c = 3·075$) [cf. Adams, Reeves, and Goebel, *loc. cit.*; m. p. 122—124°, $[\alpha]_D^{20°}$ −18·6° (acetone, $c = 1·4$)] (Found: C, 48·8; H, 8·1; OMe, 41·8. Calc. for $C_9H_{16}O_8$: C, 48·7; H, 8·1; OMe, 41·8%).

A sample (0·092 g.) was hydrolysed with hot aqueous N-hydrochloric acid (10 c.c.), and the resultant syrup (0·08 g.) in water (3 c.c.) was heated on a water-bath for 2½ hours with sodium acetate (0·3 g.) and phenylhydrazine hydrochloride (0·19 g.). On cooling, 4-methyl glucosazone (XII) was deposited: m. p. 157—158° (from benzene–ethyl alcohol) [cf. Schinle (*Ber.*, 1932, **65**, 315), m. p. 159°; Munro and Percival (J., 1935, 873), m. p. 158°].

(*b*) The nitrate (XXII) (see below) (0·242 g.) was treated with glacial acetic acid (4 c.c.) and an excess of a mixture of zinc and iron powders. Isolation in the manner described above gave a syrup (0·228 g.), free from nitrate (diphenylbenzidine test), which crystallised on standing. Recrystallisation from light petroleum–ethyl alcohol gave needles, m. p. 124°, not depressed on mixing with a sample of the product obtained in (*a*); $[\alpha]_D^{16°}$ −16·6° (acetone, $l = 2$, $c = 4·16$).

2 : 4 : 6-*Trimethyl β-Methylglucoside* 3-*Nitrate* (XIII).—The compound (V) (1·885 g.) in dry acetone (10 c.c.) was given 2 treatments in the standard manner with methyl iodide (10 c.c.) and silver oxide (10 g.). A sample (1·44 g.) of the resultant syrup, $[\alpha]_D^{12°}$ −22·1° (chloroform, $l = 2$, $c = 7·225$), gave a colourless viscous liquid (1·12 g.) on distillation, b. p. 115—120°/0·4 mm.; $n_D^{15°}$ 1·4538; $[\alpha]_D^{15°}$ −22·0° (chloroform, $l = 2$, $c = 5·526$) (Found: C, 43·0; H, 6·7; N, 5·2. $C_{10}H_{19}O_8N$ requires C, 42·7; H, 6·8; N, 5·0%).

2 : 4 : 6-*Trimethyl β-Methylglucoside* (XIV).—The nitrate (XIII) (3·69 g.) was reduced by 45 mins.' refluxing with 2N-sodium hydroxide (30 c.c.) of which half had previously been saturated with hydrogen sulphide, sufficient ethyl alcohol being added to give homogeneity. The alcohol was removed by distillation, and water added to the residue, the resultant solution being then extracted 3 times with chloroform. The chloroform solution after drying (sodium sulphate), decolorisation (norit), and distillation gave a crystalline product (2·96 g.); silky needles (from light petroleum); m. p. 70°; $[\alpha]_D^{15°}$ −27·4° (chloroform, $l = 2$, $c = 0·7285$) (Found: C, 50·7; H, 8·3; OMe, 52·1. Calc. for $C_{10}H_{20}O_6$: C, 50·8; H, 8·5; OMe, 52·5%) [cf. Oldham (*J. Amer. Chem. Soc.*, 1934, **56**, 1360), Freudenberg and Plankenhorn (*Annalen*, 1938, **536**, 257), Lake and Peat (J., 1938, 1417)].

Nitration of (XIV) (0·519 g.) in chloroform (10 c.c.) with an ice-cold mixture of fuming nitric acid (10 c.c.) and chloroform (10 c.c.) for 10 minutes at 0°, followed by isolation as for (II), gave a thin syrup (0·543 g.) having $n_D^{14°}$ 1·4540.

2-*Methyl* 4 : 6-*Ethylidene β-Methylglucoside* 3-*Nitrate* (XV).—The compound (III) (5 g.) was completely methylated after one treatment (2 hours) in acetone (5 c.c.) with methyl iodide (10 c.c.) and silver oxide (10 g.). The product (5·27 g.) had m. p. 104—106° (from ethyl alcohol) (Bell and Synge, *loc. cit.*, give m. p. 104·5—105·5°) (Found: OMe, 22·1. Calc. for $C_{10}H_{17}O_8N$: OMe, 22·2%).

2-*Methyl* 4 : 6-*Ethylidene β-Methylglucoside* (XVI).—The above nitrate (XV) (4 g.) was treated with 2N-sodium sulphide solution (30 c.c.) as for (XIV), and the product (3·41 g.) had m. p. 120° (from ethyl alcohol), $[\alpha]_D^{15°}$ −66·8° (chloroform, $l = 2$, $c = 1·60$) (Bell and Synge, *loc. cit.*, give m. p. 122—123°, $[\alpha]_D$ −66·0°) (Found: C, 51·4; H, 7·8; OMe, 26·6. Calc. for $C_{10}H_{18}O_6$: C, 51·3; H, 7·7; OMe, 26·5%).

3-*Acetyl* 2-*Methyl* 4 : 6-*Ethylidene β-Methylglucoside* (XVII).—The glucoside (XVI) (1·75 g.) on treatment with acetic anhydride (1·15 g.) in anhydrous pyridine in the cold for 12 hours gave crystals (1·6 g.), m. p. 113° (from aqueous methyl alcohol), $[\alpha]_D^{18°}$ −34·8° (chloroform, $l = 2$, $c = 3·01$) (Found: C, 51·9; H, 6·9; OMe, 22·1. $C_{12}H_{20}O_7$ requires C, 52·1; H, 7·2; OMe, 22·4%).

3-*Acetyl* 2-*Methyl β-Methylglucoside* 4 : 6-*Dinitrate* (XVIII).—The *acetyl* derivative (XVII) (1·4 g.) in dry chloroform (20 c.c.) was treated for 15 minutes at 0° with fuming nitric acid (20 c.c.) in chloroform (20 c.c.). The product (1·4 g.), after isolation as for (VIII), had m. p. 73—75° (from ethyl acetate), $[\alpha]_D^{14°}$ +20·6° (chloroform, $l = 2$, $c = 4·126$) (Found: C, 35·8; H, 4·9; OMe, 18·7. $C_{10}H_{16}O_{11}N_2$ requires C, 35·3; H, 4·7; OMe, 18·2%).

6-*Iodo* 3-*Acetyl* 2-*Methyl β-Methylglucoside* (XIX).—The *dinitrate* (XVIII) (5·561 g.) was heated with sodium iodide and acetone (35 c.c.) in a sealed tube for 16 hours at 100°. The product (5·69 g.), isolated as for (III), crystallised from light petroleum–ether (2 : 1), showing m. p. 96—97°, $[\alpha]_D^{14°}$ +19·8° (chloroform, $l = 2$, $c = 5·22$) (Found: C, 33·5; H, 4·8; I, 34·8; OMe, 17·2. $C_{10}H_{17}O_6I$ requires C, 33·3; H, 4·7; I, 35·3; OMe, 17·2%).

3-*Acetyl* 2-*Methyl β-Methylglucoside* 6-*Nitrate* (XX).—A solution in acetonitrile (20 c.c.) of the *iodo*-compound (XIX) (1·059 g.) and silver nitrate (1·2 g.) was refluxed for 2 hours; the acetonitrile was then removed by distillation, and the residue extracted several times with boiling chloroform. Removal of the solvent by distillation gave a syrup, in theoretical amount; $n_D^{19°}$ 1·4650; $[\alpha]_D^{13°}$ +1·1° (chloroform, $l = 2$, $c = 4·21$). Acetylation of a sample (0·191 g.) yielded 3 : 4-*diacetyl* 2-*methyl β-methylglucoside* 6-*nitrate* (XXIII) (0·112 g.), needles (from light petroleum), m. p. 104—105°, $[\alpha]_D^{16°}$ +9·7° (chloroform, $l = 2$, $c = 1·536$) (Found: C, 42·7; H, 5·6; N, 4·0; OMe, 18·5. $C_{12}H_{19}O_{10}N$ requires C, 42·8; H, 5·6; N, 4·1; OMe, 18·4%).

3-*Acetyl* 2 : 4-*Dimethyl β-Methylglucoside* 6-*Nitrate* (XXI).—After 2 treatments with Purdie's reagents the above compound (XX) (0·407 g.) gave a syrup (0·418 g.) which had $n_D^{19°}$ 1·4550, $[\alpha]_D^{18°}$ −5·7° (chloroform, $l = 2$, $c = 4·15$) (Found: OMe, 30·3. $C_{11}H_{19}O_9N$ requires OMe, 30·1%).

2 : 4-*Dimethyl β-Methylglucoside* 6-*Nitrate* (XXII).—Deacetylation of the foregoing *compound* by Zemplen's method proceeded very slowly. The compound (0·415 g.) in chloroform (10 c.c.) was treated with methyl alcohol (10 c.c.) containing sodium methoxide (10 mg. of sodium), the course of the reaction being followed polarimetrically. When a constant value was reached (6 days) the product was isolated in the standard manner as a syrup (0·315 g.) which could not be crystallised. It had $n_D^{18°}$ 1·4630, $[\alpha]_D^{14°}$ −15·2° (chloroform, $l = 2$, $c = 3·15$) (Found: OMe, 35·0. $C_9H_{17}O_8N$ requires OMe, 34·8%).

3-*Benzoyl* 2-*Methyl β-Methylglucoside* (XXV).—A sample of (XVI) (0·279 g.) on treatment with benzoyl chloride (0·42 c.c.) in pyridine yielded a colourless syrup (XXIV) (0·51 g.) which could not be crystallised. A mixture of this compound (0·5 g.) and aqueous alcohol (25 c.c.) containing 1% hydrochloride acid was heated under reflux for 5 hours (*i.e.*, until of constant rotation); barium carbonate was added to neutralise the acid, and, after filtration, the alcohol was removed by distillation. The residual aqueous solution was further diluted with water, and shaken twice with benzene, the extract being discarded. Much potassium chloride was then added, and the solution shaken 6 times with chloroform. After drying (sodium sulphate), the solvent was removed by distillation from the combined chloroform extracts, yielding a syrup (0·332 g.) which crystallised after some hours in contact with ether–light petroleum. Recrystallisation from benzene–light petroleum gave plates, m. p. 132—133°, $[\alpha]_D^{14°}$ +28·5° (chloroform, $l = 2$, $c = 1·42$) (Found: C, 57·7; H, 6·6; OMe, 20·2. $C_{15}H_{20}O_7$ requires C, 57·7; H, 6·4; OMe, 19·9%).

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136. *Sugar Nitrates. Part II. Synthesis of* 3 : 4-*Dimethyl Glucose:* 3-*Methyl* β-*Methylglucoside.*

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Starting from 4 : 6-ethylidene β-methylglucoside 3-nitrate, a simple synthesis of 3 : 4-dimethyl glucose was accomplished, thus completing the series of partly methylated glucoses. From the same compound, by three routes, the known 3-methyl β-methylglucoside was also obtained. A number of new derivatives of β-methylglucoside are described.

IN proceeding from 4 : 6-ethylidene β-methylglucoside 3-nitrate towards a synthesis of 3 : 4-dimethyl glucose, the 2-benzoyl derivative (I) and thence 2-benzoyl 4 : 6-ethylidene β-methylglucoside (II) were first formed. Choice of benzoyl in preference to acetyl derivatives was based on the possibility of acyl migration during methylation: this disadvantage was found to outweigh the advantages attending the use of acetyl derivatives, in that it was found that methylation of 2-acetyl 4 : 6-ethylidene β-methylglucoside (XX) failed to give a definite crystalline compound, although subsequently by other means (III ⟶ XVI ⟶ XVIII) this could be obtained. Tosyl compounds provided another alternative, but, although a series of definite crystalline tosyl derivatives (XXI, XXII, XXIII) was obtained, the route was not fully explored.

In the series of reactions described, removal of the ethylidene residue was effected in three different ways: (*a*) acid hydrolysis [(cf., *inter alia*, Ohle and Spencker, *Ber.*, 1928, **61**, 2387), (III) ⟶ (IV); (*b*) acetolysis (cf. Bell and Synge, J., 1937, 1711), (III) ⟶ (XIII); (*c*) by the use of fuming nitric acid in chloroform, (XVI) ⟶ (XVII). Method (*a*), although applicable to this class of compound [see preceding paper, (XXIV) ⟶ (XXV)], is unsuitable for ethylidene compounds having the nitrate group in position 2 or 3 (cf. Bell and Synge, *loc. cit.*). In earlier work we found that the process was effective in the case of 2-methyl ethylidene β-methylglucoside, but very slow. The syrup obtained from (III) by the use of method (*b*) was, by analogy to similar cases (Bell and Synge, *loc. cit.*), deemed to be (XIII), and gave the expected 3-methyl β-methylglucoside (XIV) on alkaline hydrolysis. The syrupy nature of the product of this reaction is in accordance with frequent experience, for our attempts to apply the reaction to a large number of ethylidene compounds have, with the exception of those described by Bell and Synge, failed to give crystalline compounds. It is noteworthy that treatment of 2-methyl 4 : 6-ethylidene β-methylglucoside 3-nitrate in this way gave a syrup, but that after some months crystals were deposited, which were however ineffective in inducing the crystallisation of a freshly prepared syrup. Analytical data for the crystalline deposit corresponded to a monoacetyl monomethyl β-methylglucoside 3-nitrate, presumably 6-*acetyl* 2-*methyl* β-*methylglucoside* 3-*nitrate* formed by decomposition of the syrup with elimination of the 4-α-acetoxyethyl group. Method (*c*) in general replaces the ethylidene group by two nitrate groups, at the same time introducing further nitrate substituents where places are available.

Complete absence of steric effect exerted by the triphenylmethyl group was observed, methylation of (V) to (VI) being effected in one treatment.

The identity of (IX) seems conclusive. It differs from the known dimethyl β-methylglucosides and therefore must be the 3 : 4-isomer, the only remaining possibility. This is in accordance with the method of synthesis, wherein, by the formation of 3-methyl β-methylglucoside by two routes from (III), the position of one of the methyl groups is confirmed.

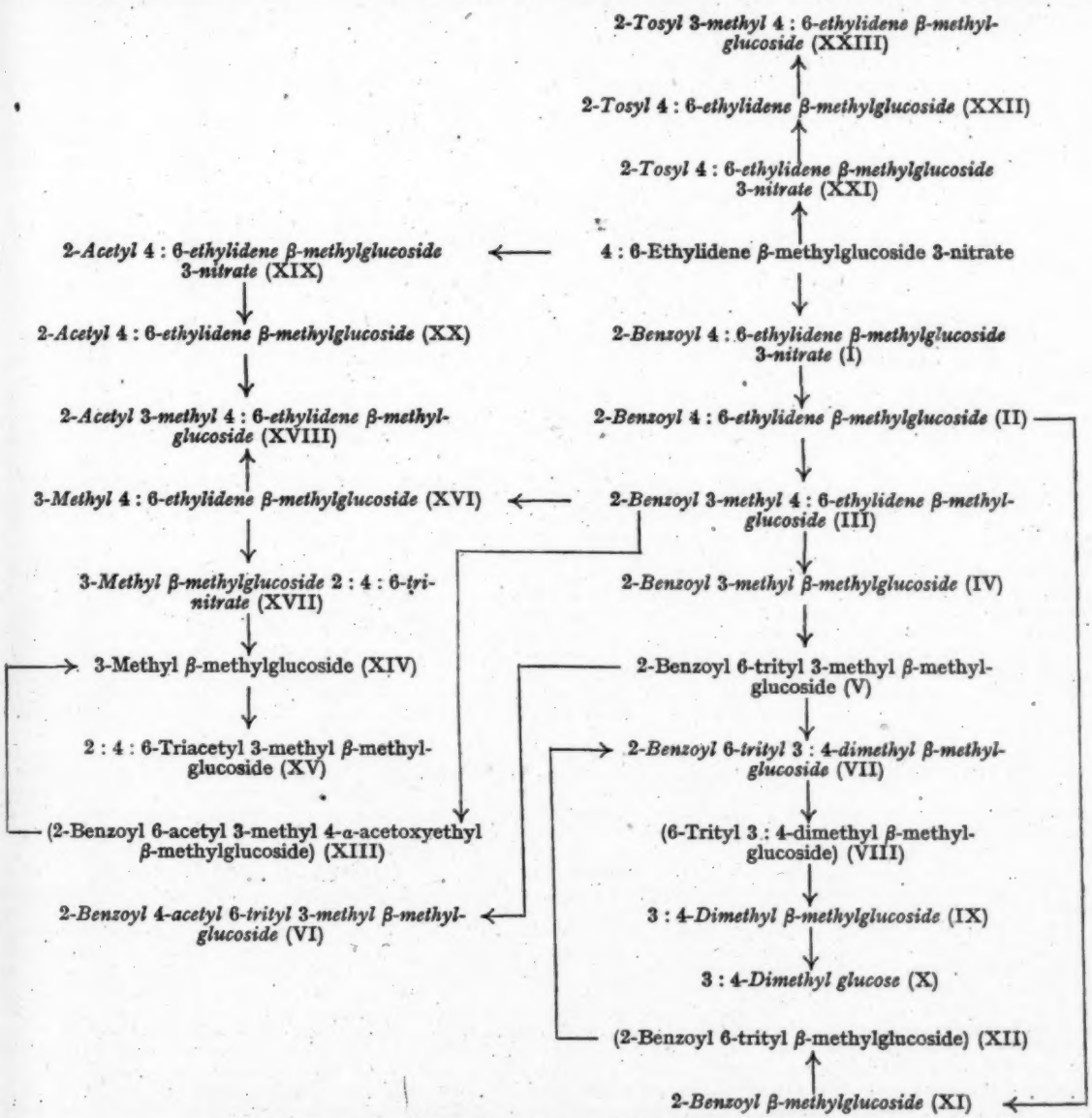
EXPERIMENTAL.

All evaporations were carried out under diminished pressure, and, unless otherwise stated, at below 50°. The light petroleum used in recrystallisations had b. p. 60—80°.

2-*Benzoyl* 4 : 6-*Ethylidene β-Methylglucoside* 3-*Nitrate* (I).—Benzoyl chloride (7·9 c.c.) was added gradually to an ice-cold solution of 6 g. of 4 : 6-ethylidene β-methylglucoside 3-nitrate (preceding paper) in dry pyridine. After 4 days at room temperature, the mixture was poured into cold water (400 c.c.), and, after the supernatant liquid had been decanted, the remaining syrup was washed with water and then dissolved in benzene. This solution was washed successively with sulphuric acid (2%), sodium hydroxide (2%), and water, and, after being dried (sodium sulphate) and decolorised (norit), the solvent was removed by distillation. The residual red-brown glass crystallised on treatment with methyl

alcohol, and after recrystallisation (methyl alcohol) yielded plates (7·05 g.), m. p. 123—124°, $[\alpha]_D^{19°}$ +19·9° (chloroform, $l = 2$, $c = 4·789$) (Found: C, 52·5; H, 5·2; N, 3·9; OMe, 8·4. $C_{16}H_{19}O_8N$ requires C, 52·0; H, 5·2; N, 3·8, OMe, 8·4%).

2-Benzoyl 4 : 6-*Ethylidene* β-*Methylglucoside* (II).—The above *compound* (1·872 g.) in glacial acetic acid (20 c.c.) was treated with a mixture of iron and zinc powders, the system being kept cold by immersion in water. In 15 minutes the reaction was complete (diphenylamine test) and the mixture was filtered, the residue well washed with chloroform, and the washings added to the filtrate. This chloroform–acetic acid solution was shaken with water, and the aqueous layer extracted with chloroform. After the combined chloroform extracts had been dried (sodium sulphate and potassium carbonate), the solvent was removed by distillation, yielding a crystalline product (1·597 g.). Recrystallisation


2-Tosyl 3-methyl 4 : 6-ethylidene β-methylglucoside (XXIII)
2-Tosyl 4 : 6-ethylidene β-methylglucoside (XXII)
2-Tosyl 4 : 6-ethylidene β-methylglucoside 3-nitrate (XXI)
2-Acetyl 4 : 6-ethylidene β-methylglucoside 3-nitrate (XIX)
4 : 6-Ethylidene β-methylglucoside 3-nitrate
2-Acetyl 4 : 6-ethylidene β-methylglucoside (XX)
2-Benzoyl 4 : 6-ethylidene β-methylglucoside 3-nitrate (I)
2-Acetyl 3-methyl 4 : 6-ethylidene β-methylglucoside (XVIII)
2-Benzoyl 4 : 6-ethylidene β-methylglucoside (II)
3-Methyl 4 : 6-ethylidene β-methylglucoside (XVI)
2-Benzoyl 3-methyl 4 : 6-ethylidene β-methylglucoside (III)
3-Methyl β-methylglucoside 2 : 4 : 6-trinitrate (XVII)
2-Benzoyl 3-methyl β-methylglucoside (IV)
3-Methyl β-methylglucoside (XIV)
2-Benzoyl 6-trityl 3-methyl β-methylglucoside (V)
2 : 4 : 6-Triacetyl 3-methyl β-methylglucoside (XV)
2-Benzoyl 6-trityl 3 : 4-dimethyl β-methylglucoside (VII)
(2-Benzoyl 6-acetyl 3-methyl 4-α-acetoxyethyl β-methylglucoside) (XIII)
(6-Trityl 3 : 4-dimethyl β-methylglucoside) (VIII)
2-Benzoyl 4-acetyl 6-trityl 3-methyl β-methylglucoside (VI)
3 : 4-Dimethyl β-methylglucoside (IX)
3 : 4-Dimethyl glucose (X)
(2-Benzoyl 6-trityl β-methylglucoside) (XII)
2-Benzoyl β-methylglucoside (XI)

(Compounds in parenthesis have not been characterised.)

from ethyl alcohol–light petroleum gave plates, m. p. 190—191°, $[\alpha]_D^{19°}$ −39·5° (chloroform, $l = 2$, $c = 4·927$) (Found: C, 59·4; H, 6·2; OMe, 9·6. $C_{16}H_{20}O_7$ requires C, 59·3; H, 6·2; OMe, 9·6%).

2-Benzoyl 3-*Methyl* 4 : 6-*Ethylidene* β-*Methylglucoside* (III).—The above *compound* (II) (1·004 g.) in dry acetone (5 c.c.) after one treatment for 4 hours with methyl iodide (10 c.c.) and silver oxide (10 g.) showed the theoretical increase in weight, and removal of the solvent by distillation yielded crystals, which after recrystallisation (ethyl alcohol–light petroleum) gave plates (0·726 g.), m. p. 159°, $[\alpha]_D^{19°}$ −2·1° (chloroform, $l = 2$, $c = 3·888$) (Found: C, 60·4; H, 6·5; OMe, 18·4. $C_{17}H_{22}O_7$ requires C, 60·4; H, 6·5; OMe, 18·4%).

2-Benzoyl 3-*Methyl* β-*Methylglucoside* (IV).—Hydrolysis of the foregoing *compound* (III) was effected by the use of 1% hydrogen chloride in aqueous 75% (v/v) ethyl alcohol. A solution of the compound (0·416 g.) in the acid mixture (25 c.c.) was heated under reflux, the reaction being followed polarimetrically. The rotation changed from an initial negative to a constant positive value (7 hours), at which point excess of calcium carbonate was added, and the solution

filtered. Most of the alcohol was removed by distillation, and the aqueous solution was diluted with water and extracted with benzene, the extract being washed with water. The combined aqueous solution, after addition of sodium chloride, was extracted 6 times with chloroform, and evaporation of the dried (sodium sulphate), combined extracts gave a crystalline residue (0·331 g.). Recrystallisation (ethyl alcohol–light petroleum) gave needles, m. p. 142—143°, $[\alpha]_D^{14°}$ +5·1° (ethyl alcohol, $l = 2$, $c = 1·876$), $[\alpha]_D^{14°}$ +15·2° (acetone, $l = 2$, $c = 5·468$) (Found: C, 57·6; H, 6·5; OMe, 19·4. $C_{18}H_{28}O_7$ requires C, 57·7; H, 6·4; OMe, 19·9%).

2-Benzoyl 6-Trityl 3-Methyl β-Methylglucoside (V).—The above *compound* (IV) (0·445 g.) was heated with trityl chloride (0·386 g.; *i.e.*, 97% of the theoretical amount) in pyridine (5 c.c.; dried over phosphoric oxide) for 2 hours in a tightly-stoppered flask on a boiling water-bath. The gum which separated on pouring into water was dissolved in benzene, and the resulting solution was washed in turn with water, dilute sulphuric acid, dilute sodium hydroxide, and water. After drying (sodium sulphate) and removal of solvent by distillation, a yellow glass (0·625 g.) which could not be crystallised was obtained. It showed $[\alpha]_D^{13°}$ −8·9° (chloroform, $l = 2$, $c = 3·03$).

2-Benzoyl 4-Acetyl 6-Trityl 3-Methyl β-Methylglucoside (VI).—Acetylation of the compound (V) (0·603 g.) with acetic anhydride (0·2 c.c.) in pyridine yielded silky needles (0·605 g.; from ethyl alcohol), m. p. 175°, $[\alpha]_D^{14°}$ +32·0° (chloroform, $l = 2$, $c = 2·092$) (Found: C, 72·6; H, 6·2; OMe, 10·2. $C_{37}H_{36}O_8$ requires C, 72·8; H, 6·2; OMe, 10·2%).

2-Benzoyl 6-Trityl 3 : 4-Dimethyl β-Methylglucoside (VII).—(*a*) One treatment (4 hours) with methyl iodide (10 c.c.) and silver oxide (10 g.) sufficed to methylate (V) (1·818 g.). Recrystallisation from methyl alcohol gave needles (67% yield), m. p. 142°, $[\alpha]_D^{14°}$ +36·4° (chloroform, $l = 2$, $c = 4·376$) (Found: C, 73·9; H, 6·5; OMe, 16·3. $C_{35}H_{36}O_7$ requires C, 73·9; H, 6·3; OMe, 16·4%).

(*b*) Methylation of (XII) (0·76 g.) with methyl iodide (10 c.c.) and silver oxide (7 g.) gave, after one treatment, a crystalline product (from methyl alcohol), m. p. 141—142° undepressed on admixture with the product in (*a*).

6-Trityl 3 : 4-Dimethyl β-Methylglucoside (VIII).—The benzoyl compound (VII) (1·975 g.) in absolute methyl alcohol (30 c.c.) was treated with sodium methoxide (0·2 g. of sodium in 5 c.c. of absolute methyl alcohol) at 100° for a few minutes; water was then added, and the solution concentrated by distillation until free from methyl benzoate. On evaporating to dryness a chloroform extract of the residue, a non-crystallisable glass (0·787 g.) was obtained; $[\alpha]_D^{18°}$ +14·2° (chloroform, $l = 2$, $c = 3·765$).

3 : 4-Dimethyl β-Methylglucoside (IX).—The trityl compound (VIII) (0·733 g.) in dry benzene (15 c.c.) (α_D +0·46° in a 2-dm. tube) was treated with dry hydrogen chloride for 30 minutes (constant α_D −0·24°). The reaction mixture was shaken with water containing sodium acetate and thereafter the aqueous layer was extracted twice with benzene (to complete the removal of tritylcarbinol). Sufficient potassium carbonate was dissolved in the aqueous solution to make this only slightly less dense than chloroform, with which the aqueous solution was extracted 12 times. Removal of the solvent by distillation from the combined extracts gave a syrup (0·334 g.) free from trityl compounds (sulphuric acid test). Further purification was effected by dissolving the syrup in water, extracting the solution 3 times with chloroform, and evaporating it to dryness; the crystalline residue weighed 0·294 g. (82% yield). In subsequent larger-scale preparations, the latter purification was omitted and the crude product was distilled (b. p. 165—169°/0·8 mm.) to yield crystals, which, after recrystallisation from acetone or carbon tetrachloride, had m. p. 79—81°, $[\alpha]_D^{15°}$ −10·9° (acetone, $l = 2$, $c = 5·3820$), −9·3° (ethyl alcohol, $l = 2$, $c = 5·2520$), −11·9° (chloroform, $l = 2$, $c = 5·3751$) (Found: C, 48·8; H, 8·2; OMe, 41·2. $C_8H_{16}O_6$ requires C, 48·7; H, 8·1; OMe, 41·8%).

3 : 4-Dimethyl Glucose (X).—The *glucoside* (IX) (0·64 g.) was treated with 2N-hydrochloric acid on a boiling water-bath until a constant rotation was observed (4 hours). An excess of lead carbonate was added, and, after filtration, the solvent was removed by evaporation. The residue was extracted several times with boiling ethyl alcohol, and the combined solutions taken to dryness. Extraction of the residual syrup with hot ethyl acetate and subsequent evaporation gave a crystalline residue (0·55 g.) which readily reduced Fehling's solution; it was further purified by recrystallisation from propyl acetate; m. p. 113°; $[\alpha]_D^{15°}$ +94·5° (8 mins.), $[\alpha]_D^{17°}$ +99·5° (48 hours) (ethyl alcohol, $l = 1$, $c = 2·04$); $[\alpha]_D^{16°}$ +88·5° (6 mins.), $[\alpha]_D^{17°}$ +102·2° (24 hours) (methyl alcohol, $l = 1$, $c = 1·984$); $[\alpha]_D^{16°}$ +64·9° (10 mins.), +94·8° (24 hours) (water, $l = 1$, $c = 0·971$) (Found: C, 46·5; H, 7·5; OMe, 29·1. $C_8H_{14}O_6$ requires C, 46·2; H, 7·7; OMe, 29·8%).

2-Benzoyl β-Methylglucoside (XI).—A solution of the compound (II) (1·614 g.) in aqueous 75% ethyl alcohol (30 c.c.) containing 1% hydrochloric acid was heated in the manner described for the conversion of (III) into (IV), a constant rotation being observed after 3 hours. After neutralisation with calcium carbonate, filtration, and evaporation to dryness, the residue was extracted with hot acetone–chloroform (2 : 1); evaporation of this solution gave crystals (1·378 g.), from which (*ex* alcohol–light petroleum) needles were obtained, m. p. 174—177°, $[\alpha]_D^{13°}$ −1·8° (acetone, $l = 4$, $c = 1·77$) (Found: C, 56·5; H, 6·1; OMe, 10·6. $C_{14}H_{18}O_7$ requires C, 56·4; H, 6·0; OMe, 10·4%).

2-Benzoyl 6-Trityl β-Methylglucoside (XII).—Treatment of the above *compound* (XI) (0·51 g.) with trityl chloride 0·453 g.; 95% of the theoretical amount) in pyridine (5 c.c.), as described for the compound (V), gave a colourless glass ((0·765 g.), $[\alpha]_D^{12°}$ −25·8° (chloroform, $l = 2$, $c = 3·8$).

2-Benzoyl 6-Acetyl 3-Methyl 4-α-Acetoxyethyl β-Methylglucoside (XIII).—After the rotation (−0·170°) of a solution of pure (III) (0·512 g.) in acetic anhydride (10 c.c.) had been observed, a drop of concentrated sulphuric acid was added and the course of the reaction followed polarimetrically (cf. Bell and Synge, *loc. cit.*). When a constant value (+2·98°) was reached (30 mins.), the solution was poured into water (70 c.c.) containing a little sodium acetate and shaken. The solution was then extracted with benzene, the benzene layer washed with potassium hydrogen carbonate solution, and the dried (sodium sulphate) solution evaporated to dryness; it gave a colourless syrup (0·596 g.) which did not crystallise.

3-Methyl β-Methylglucoside (XIV).—(*a*) The compound (XIII) (0·548 g.) in absolute methyl alcohol (5 c.c.) was heated on a water-bath with a solution of sodium (0·092 g.) in methyl alcohol (5 c.c.) for 5 minutes, the calculated amount (0·230 c.c.) of glacial acetic acid and water (10 c.c.) added, and the solution concentrated by distillation to remove all the methyl alcohol and methyl benzoate. The residual aqueous solution was shaken 3 times with chloroform (to remove unchanged material), decolourised (norit), and evaporated to dryness. Extraction with hot acetone and subsequent evaporation of the filtered extract gave a syrup (0·243 g.), $[\alpha]_D^{14°}$ −25·3° (water, $l = 2$, $c = 1·59$) (Found: OMe, 13·5. Calc. for $C_8H_{16}O_6$: OMe, 13·4%). Helferich and Lang (*J. pr. Chem.*, 1932, **132**, 321) give $[\alpha]_D^{20°}$ −26·9° (water).

(*b*) A sample of (XVII) (0·629 g.) in glacial acetic acid (7 c.c.) was reduced by an excess of zinc and iron powders, the reaction vessel being heated over a free flame. Cessation of the evolution of brown fumes indicated the completion of the reaction, and the absence of nitrate was confirmed by the diphenylbenzidine test. The reaction mixture was then poured into water–acetone (1 : 4) containing calcium carbonate; after being stirred until the evolution of carbon dioxide ceased, the solution was filtered and evaporated to dryness. The residue was extracted with acetone, and, after filtering, the solvent was distilled off, leaving a syrup (0·226 g.). Further purification was effected as in (*a*), and the resultant syrup (0·159 g.) was identical in its characteristics with the product in (*a*) and gave the same triacetate (see below).

2 : 4 : 6-Triacetyl 3-Methyl β-Methylglucoside (XV).—Treatment of (XIV) (0·221 g.) with acetic anhydride (0·6 c.c.) in pyridine (6 c.c.) gave a crystalline product (0·344 g.) forming, from light petroleum–ethyl alcohol, needles, m. p. 91·5°; $[\alpha]_D^{14°}$ −36·4° (chloroform, $l = 2$, $c = 1·856$) (Found: C, 50·3; H, 6·6; OMe, 18·2. Calc. for $C_{14}H_{22}O_9$: C, 50·3; H, 6·6; OMe, 18·5%). Helferich and Lang (*loc. cit.*) give m. p. 90—90·5°, $[\alpha]_D^{20°}$ −34·8° (chloroform).

3-Methyl 4 : 6-*Ethylidene* β-*Methylglucoside* (XVI).—The compound (III) (1·01 g.) in absolute methyl alcohol (30 c.c.) was treated with sodium methoxide (0·2 g. of sodium in 5 c.c. of absolute methyl alcohol) on a boiling water-bath for a few minutes: water was then added, and the solution concentrated by distillation until free from methyl benzoate. The aqueous residue was diluted with water and then shaken 4 times with chloroform; the chloroform solution was dried (sodium sulphate) and evaporated, giving a crystalline product (0·661 g.); needles (*ex* light petroleum–ethyl alcohol), m. p. 134°; $[\alpha]_D^{19°}$ −43·7° (chloroform, $l = 2$, $c = 4·642$) (Found: C, 51·3; H, 7·6; OMe, 26·2 $C_{10}H_{18}O_6$ requires C, 51·3; H, 7·7; OMe, 26·5%).

3-Methyl β-*Methylglucoside* 2 : 4 : 6-*Trinitrate* (XVII).—To an ice-cold solution of (XVI) (0·638 g.) in chloroform (15 c.c.) was added a cold mixture of fuming nitric acid (20 c.c.) and chloroform (20 c.c.); after 15 minutes at 0° the mixture was poured into ice and water and shaken rapidly. The chloroform solution was then washed with sodium hydrogen carbonate solution, dried with sodium sulphate, and evaporated. The resultant syrup (0·856 g.) crystallised rapidly; recrystallised from methyl alcohol, it formed needles, m. p. 56—57°, $[\alpha]_D^{14°}$ −1·6° (chloroform, $l = 2$, $c = 1·841$). The *nitrate* was mildly explosive above its m. p. (Found: C, 28·7; H, 3·8; N, 12·1; OMe, 18·1. $C_9H_{13}O_{12}N_3$ requires C, 28·0; H, 3·8; N, 12·3; OMe, 18·1%).

2-Acetyl 3-Methyl 4 : 6-*Ethylidene* β-*Methylglucoside* (XVIII).—(*a*) The compound (XVI) (0·678 g.) was acetylated by treatment with acetic anhydride (0·413 c.c.) in anhydrous pyridine (10 c.c.) for 2 days at room temperature. Isolation by extraction with chloroform, the extract being washed in the usual manner, gave, on distillation of the solvent, a crystalline residue (0·811 g.), m. p. 101—103° (*ex* light petroleum), $[\alpha]_D^{17°}$ −41·2° (chloroform, $l = 2$, $c = 2·831$) (Found: C, 52·3; H, 6·8; OMe, 22·5. $C_{12}H_{20}O_7$ requires C, 52·1; H, 7·2; OMe, 22·5%).

(*b*) One methylation by Purdie's method of a sample of (XX) (0·516 g.) gave a syrup (0·52 g.), which crystallised immediately on nucleation with the product obtained as in (*a*). After recrystallisation as in (*a*), the m. p. was 101—103°, unaltered on mixing with a sample from (*a*) but depressed by 3-acetyl 2-methyl 4 : 6-ethylidene β-methylglucoside (m. p. 113°; preceding paper).

2-Acetyl 4 : 6-*Ethylidene* β-*Methylglucoside* 3-*Nitrate* (XIX).—4 : 6-Ethylidene β-methylglucoside 3-nitrate (2 g.) in pyridine was treated with acetic anhydride (1·05 c.c.) for 24 hours at room temperature. Isolation in the usual way by means of benzene gave a crystalline product (2·26 g.), m. p. 129—130°, $[\alpha]_D^{21°}$ −44·8° (chloroform, $l = 2$, $c = 5·2$) (Found: C, 43·0; H, 5·4; N, 4·9; OMe, 10·1. $C_{11}H_{17}O_8N$ requires C, 43·0; H, 5·6; N, 4·6; OMe, 10·1%).

2-Acetyl 4 : 6-*Ethylidene* β-*Methylglucoside* (XX).—(*a*) A solution of (XIX) (1·915 g.) in acetone (40 c.c.) and water (1 c.c.) was shaken mechanically with liquid zinc amalgam for 5 hours (negative test for nitrate with diphenylbenzidine) and then filtered. On removal of solvent by evaporation, a glass (1·802 g.) was obtained; this was dissolved in chloroform, and the solution washed several times with water. After drying (sodium sulphate), the chloroform was distilled off, giving a glass (1·04 g.) which did not crystallise; $[\alpha]_D^{15°}$ −52·8° (chloroform, $l = 2$, $c = 3·196$) (Found: OMe, 11·9; Ac, 16·4. $C_{11}H_{16}O_7$ requires OMe, 11·8; Ac, 16·4%).

(*b*) The same product with identical characteristics was also obtained by reducing a sample of (XIX) (0·863 g.) in glacial acetic acid (15 c.c.) with equal parts of zinc and iron powders. The yield (0·705 g.) was 96%, in contrast to 64% from (*a*).

2-Tosyl 4 : 6-*Ethylidene* β-*Methylglucoside* 3-*Nitrate* (XXI).—A 50% excess of *p*-toluenesulphonyl chloride (5·02 g.) was added to a solution of 4 : 6-ethylidene β-methylglucoside 3-nitrate (4·66 g.) in dry pyridine (16 c.c.), and, after shaking, the mixture was left at room temperature for 6 days. Isolation in the standard manner gave crystals (6·195 g.), m. p. 136—139°. The pure *substance*, m. p. 143—144°, $[\alpha]_D^{19°}$ −10·3° (chloroform, $l = 2$, $c = 5·429$), was obtained by recrystallisation from methyl alcohol (Found: C, 45·9; H, 5·1; N, 3·5; OMe, 7·4. $C_{18}H_{21}O_{10}NS$ requires C, 45·8; H, 5·1; N, 3·3; OMe, 7·4%).

2-Tosyl 4 : 6-*Ethylidene* β-*Methylglucoside* (XXII).—A warm solution of this nitrate (6·205 g.) in glacial acetic acid (50 c.c.) was treated with zinc and iron powders for 10 minutes and the product isolated as before (I → II). The resultant syrup (5·45 g., n_D 1·5140) crystallised on standing, and the pure material (plates, *ex* light petroleum–ethyl alcohol) had m. p. 152—153°, $[\alpha]_D^{18°}$ −45·5° (chloroform, $l = 2$, $c = 3·385$) (Found: C, 51·7; H, 5·8; OMe, 8·2. $C_{16}H_{22}O_8S$ requires C, 51·3; H, 5·9; OMe, 8·3%).

2-Tosyl 3-Methyl 4 : 6-*Ethylidene* β-*Methylglucoside* (XXIII).—Treatment of (XXII) (1·001 g.) in acetone (5 c.c.) with methyl iodide (10 c.c.) and silver oxide (10 g.) for 4 hours gave a syrup (theoretical yield) which crystallised in contact with methyl alcohol. The pure *substance* (*ex* light petroleum–ethyl alcohol) had m. p. 123—124°, $[\alpha]_D^{22°}$ −22·8° (chloroform, $l = 2$, $c = 3·885$) (Found: C, 52·3; H, 6·0; OMe, 15·5. $C_{17}H_{24}O_8S$ requires C, 52·6; H, 6·2; OMe, 16·0%).

Acetolysis of 2-*Methyl* 4 : 6-*Ethylidene* β-*Methylglucoside* 3-*Nitrate* [Bell and Synge (*loc. cit.*); Dewar and Fort (*loc. cit.*)].—The nitrate (2·5 g.) was dissolved in acetic anhydride (50 c.c.), concentrated sulphuric acid (0·05 c.c.) added, and the course of the reaction followed polarimetrically [α_D (5 mins.) + 0·92° ($l = 2$)]. After 50 mins. [(α_D +3·47° ($l = 2$)], the solution was shaken with ice-water (250 c.c.) containing some sodium acetate. The whole was then extracted 3 times with benzene, and the extract washed with sodium hydrogen carbonate solution, dried (sodium sulphate), and evaporated, giving a syrup (3·4 g.; $n_D^{16°}$ 1·4590) (Found: OMe, 15·2. Calc. for 6-acetyl 2-methyl 4-α-acetoxyethyl β-methylglucoside 3-nitrate, $C_{14}H_{23}O_{11}N$: OMe, 16·3%). Attempts to crystallise freshly prepared material failed, but, after several months, crystals were formed; m. p. 130—132° (*ex* methyl alcohol), $[\alpha]_D^{16°}$ −47·0° (chloroform, $l = 2$, $c = 1·8$) (Found: C, 40·8; H, 5·8; N, 4·7; OMe 20·8. Calc. for a monoacetyl monomethyl methylglucoside mononitrate, $C_{10}H_{17}O_8N$: C, 40·7; H, 5·8; N, 4·7; OMe, 21·0%). Freshly prepared syrup could not be induced to crystallise by nucleation with this crystalline product.

The authors acknowledge their indebtedness to the Carnegie Trust for the grant of a Scholarship which enabled one of them (G. F.) to take part in this and the preceding investigation, and to Dr. J. W. H. Oldham (Royal Institution) for his interest and kindly criticism.

THE UNIVERSITY, ST. ANDREWS. [*Received, June 13th*, 1944.]

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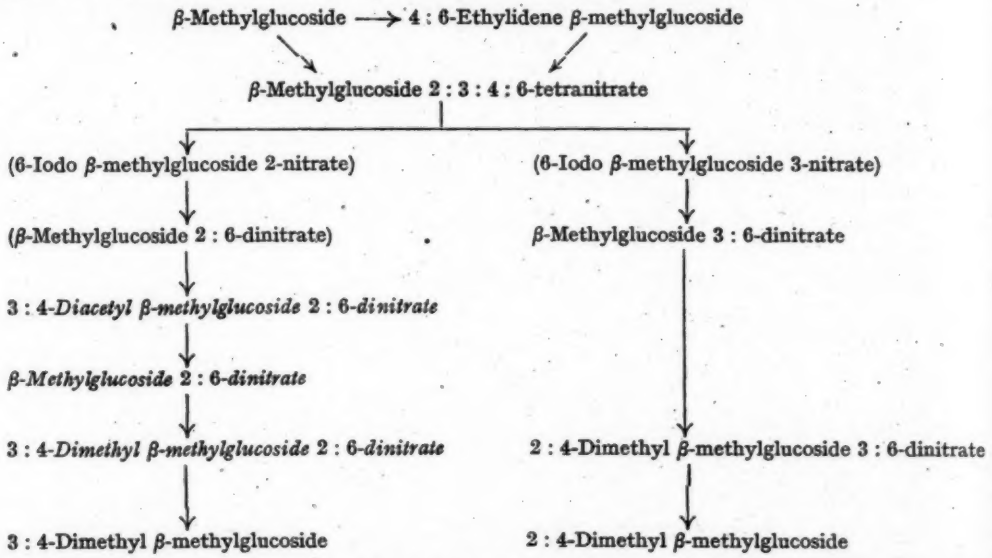
137. *Sugar Nitrates. Part III.* 2 : 4-*Dimethyl* β-*Methylglucoside and* 3 : 4-*Dimethyl* β-*Methylglucoside from* β-*Methylglucoside* 2 : 3 : 4 : 6-*Tetranitrate.*

By JOHN DEWAR, GODFREY FORT, and NORMAN MCARTHUR.

By treating β-methylglucoside 2 : 3 : 4 : 6-tetranitrate successively with sodium iodide (in acetone) and silver nitrate (in acetonitrile), β-methylglucoside 3 : 6- and 2 : 6-dinitrate are obtained, and these can readily be converted into 2 : 4- and 3 : 4-dimethyl β-methylglucoside respectively.

THE action of sodium iodide on 4 : 6-ethylidene β-methyglucoside 2 : 3-dinitrate causes the nitrate group in position 2 to be replaced by hydroxyl (Dewar and Fort, this vol., p. 492) and the same reaction applied to 2 : 3-dimethyl β-methylglucoside 4 : 6-dinitrate (Oldham and Rutherford, *J. Amer. Chem. Soc.*, 1932, **54**, 366) leads to the corresponding 6-iodo-4-hydroxy-compound as the principal product. It was thus of interest to examine the effect on a single compound in which nitrate groups occupied all four available positions (*e.g.*, β-methylglucoside 2 : 3 : 4 : 6-tetranitrate) in the expectation that the product would consist largely of the 6-iodo-derivative of the 3-nitrate. Evidence has been obtained that this compound is formed, but is accompanied by a greater proportion of a product derived from the 6-iodo-2-nitrate.


β-Methylglucoside
4 : 6-Ethylidene β-methylglucoside
β-Methylglucoside 2 : 3 : 4 : 6-tetranitrate
(6-Iodo β-methylglucoside 2-nitrate)
(6-Iodo β-methylglucoside 3-nitrate)
(β-Methylglucoside 2 : 6-dinitrate)
β-Methylglucoside 3 : 6-dinitrate
3 : 4-Diacetyl β-methylglucoside 2 : 6-dinitrate
β-Methylglucoside 2 : 6-dinitrate
3 : 4-Dimethyl β-methylglucoside 2 : 6-dinitrate
2 : 4-Dimethyl β-methylglucoside 3 : 6-dinitrate
3 : 4-Dimethyl β-methylglucoside
2 : 4-Dimethyl β-methylglucoside

Treatment of a 6-iodo-compound with silver nitrate in acetonitrile yields the corresponding 6-nitrate (Oldham and Rutherford, *loc. cit.*) and it was found better to utilise this reaction than to isolate the iodine derivatives. Fractionation by partition experiments followed, and crystalline β-methylglucoside 3 : 6-dinitrate (cf. Dewar and Fort, *loc. cit.*) was separated. Acetylation of the syrupy residue yielded a crystalline diacetyl dinitrate, for which (on the assumption that one of the nitrate groups occupied position 6) the following were possible structures: (*a*) 2 : 3-diacetyl 4 : 6-dinitrate, (*b*) 2 : 4-diacetyl 3 : 6-dinitrate, (*c*) 3 : 4-diacetyl 2 : 6-dinitrate. For comparison, a sample of (*a*) was prepared (Oldham and Rutherford, *loc. cit.*; Bell and Synge, J., 1937, 1711), and determinations of m. p., mixed m. p., and optical rotation provided conclusive evidence of non-identity. Similarly, structure (*b*) was rejected (cf. Dewar and Fort, *loc. cit.*), and confirmation of (*c*) was obtained by deacetylating, methylating, and then denitrating it to give the known 3 : 4-dimethyl β-methylglucoside (Dewar and Fort, *loc. cit.*). Likewise, methylation and subsequent denitration of β-methylglucoside 3 : 6-dinitrate yielded 2 : 4-dimethyl β-methylglucoside (Dewar and Fort, *loc. cit.*).

It is possible therefore to obtain the 2 : 4-dimethyl and the 3 : 4-dimethyl derivative of β-methylglucoside from this material by these few operations and all but one stage give high yields of products, only the sodium iodide reaction being variable in this respect.

EXPERIMENTAL.

All evaporations were carried out under diminished pressure, and, unless otherwise stated, at below 50°. The light petroleum used in recrystallisations was that of b. p. 60—80°.

β-Methylglucoside 2 : 3 : 4 : 6-Tetranitrate (cf. Brough and Dewar, *J. Soc. Chem. Ind.*, 1936, **55**, 207 T; Bell and Synge, *loc. cit.*).—(*a*) To an ice-cold solution of β-methylglucoside (2 g.) in dry chloroform (10 c.c.) was added an ice-cold solution of fuming nitric acid (15 c.c.) in chloroform (15 c.c.); after 15 mins. at 0°, the reaction mixture was poured into ice and water, rapidly shaken, and the chloroform layer separated. This was washed with potassium hydrogen carbonate solution, dried (sodium sulphate), and, on removal of solvent by distillation, a crystalline product (average yield, 69%) was obtained. Recrystallisation from methyl alcohol gave pure nitrate, m. p. 116—117°.

(*b*) Nitration of 4 : 6-ethylidene β-methylglucoside (2 g.) as in (*a*) gave needles (1·4 g.), m. p. 116—117° (*ex* methyl alcohol). A mixture of the products from (*a*) and (*b*) melted sharply at 116—117°. The tetranitrate burned rapidly when heated above its m. p., and exploded violently if confined in a m. p. tube sealed at both ends and heated cautiously.

Treatment of β-Methylglucoside 2 : 3 : 4 : 6-Tetranitrate with Sodium Iodide in Acetone.—The following are representative of many different experiments. (*a*) The tetranitrate (2·8 g.), sodium iodide (5·6 g.), and acetone (35 c.c.) were heated for 2 hours in a sealed tube at 100°. Isolation in the standard manner gave a syrup (2·15 g.) from which iodine was evolved on warming a sample with concentrated sulphuric acid. The syrup was dissolved in benzene and extracted four times with water, the last extract being optically inactive. The combined aqueous solutions were saturated with potassium carbonate and extracted four times with acetone, the last extract being without rotation. From the dried benzene solution on evaporation there was obtained a syrup (1·05 g.), which did not crystallise (Found: OMe, 10·2; I, 9·4%). Evaporation of the dried acetone solution gave a syrup (1·06 g.) which did not crystallise (Found:

OMe, 8·6; I, 7·1. Calc. for tri-, di-, and mono-nitrate of 6-iodo β-methylglucoside, respectively: OMe, 7·1, 7·9, 8·9; I, 28·9, 32·2, 36·4%).

(*b*) The tetranitrate (3·4 g.), sodium iodide (6·8 g.), and acetone (30 c.c.) were heated for 14 hours in a sealed tube at 100°; the acetone was distilled off, an almost saturated solution of potassium carbonate added, and the whole extracted 6 times with chloroform. After drying (sodium sulphate), the solvent was distilled off from the combined chloroform solutions, yielding a syrup (2·08 g.). A benzene solution of this was shaken 6 times with water and the combined aqueous solutions, after one wash with benzene, were then extracted 6 times with chloroform. Thereafter, much potassium carbonate was added to the aqueous solution, which was then extracted 6 times with chloroform, and these chloroform extracts, after drying (sodium sulphate), were distilled, giving a syrup (0·933 g.) which would not crystallise. A sample of this syrup (0·885 g.) was treated with silver nitrate (1·08 g.) in acetonitrile (10 c.c.) at 90° for 2 hours. After separation of the precipitated silver iodide, the solvent was distilled off, and the residual syrup extracted several times with boiling chloroform. The solution was decolorised (norit) and then distilled, giving a syrup (0·644 g.) showing a positive test for nitrate and a negative test for iodine (Found: OMe, 12·9%). Partial crystallisation set in after several days, and crystals (0·1 g.) were separated by washing with chloroform, in which the syrupy constituent (X) readily dissolved. The crystals had m. p. 144—146° and did not depress the m. p. of an authentic sample of β-methylglucoside 3 : 6-dinitrate (Dewar and Fort, *loc. cit.*).

The syrup (X) (0·285 g.) on treatment with acetic anhydride (0·56 g.) in pyridine (4 c.c.) for 3 days at room temperature, gave, on isolation in the usual manner, a syrup (0·284 g.), from which, on addition of a small amount of ethyl alcohol, crystals (0·135 g.) separated. Recrystallisation from light petroleum–alcohol gave needles, m. p. 128—129°, of 3 : 4-*diacetyl β-methylglucoside* 2 : 6-*dinitrate* (Found: C, 36·1; H, 4·3; N, 7·5; OMe, 8·7. $C_{11}H_{16}O_{12}N_2$ requires C, 35·9; H, 4·3; N, 7·6; OMe, 8·4%). When admixed with 2 : 3-diacetyl β-methylglucoside 4 : 6-dinitrate, m. p. 120—121°, the m. p. was depressed to 100—108°.

(*c*) The tetranitrate (6·38 g.), sodium iodide (12·8 g.), and acetone (30 c.c.) were heated for 19 hours in a sealed tube at 100°; the solvent was then distilled off and the residue shaken with chloroform and a concentrated solution of potassium carbonate, containing a little sodium thiosulphate. In all, 12 extractions with chloroform were carried out and, after drying (sodium sulphate) and decolorising (norit), the solvent was distilled from the combined chloroform solutions. The resultant syrup (4·14 g.) was now heated at 100° for 2 hours with silver nitrate (4 g.) in acetonitrile (25 c.c.), and then, after filtration, the solvent was removed by distillation. The residue was extracted several times with small volumes of boiling chloroform, and evaporation of these extracts gave a syrup (2·732 g.), which did not contain iodine. To effect a separation, this syrup was shaken with benzene and water, 3 extractions with benzene being carried out. Evaporation of the dried (sodium sulphate) benzene extract gave a syrup (P) (0·323 g.). The aqueous solution from the previous extraction process with benzene was then extracted 3 times with chloroform, and evaporation of the combined, dried (sodium sulphate) solutions gave a syrup (Q) (0·36 g.). Potassium carbonate was now added to the aqueous solution until this was only slightly less dense than chloroform, and 12 extractions were carried out with this solvent. Evaporation of these combined chloroform solutions gave a syrup (R) (1·43 g.).

Residue (R) crystallised partly on addition of chloroform, and the crystalline material was filtered off, washed with chloroform, and recrystallised from chloroform–ethyl alcohol, giving pure β-methylglucoside 3 : 6-dinitrate (0·335 g.), m. p. 145—147°, $[\alpha]_D^{20°}$ − 7·8° (acetone, $l = 2$, $c = 4·7$). Evaporation of the chloroform washings gave a syrup, a sample of which (1·029 g.) was acetylated in the standard manner to give crystals (1·085 g.) {needles (*ex* light petroleum–ethyl alcohol), m. p. 128—129°, $[\alpha]_D^{13°}$ + 5·8° (chloroform, $l = 2$, $c = 5·932$)} of 3 : 4-diacetyl β-methylglucoside 2 : 6-dinitrate.

The syrup (Q) (0·36 g.) on acetylation gave a syrup (0·19 g.) from which by treatment with light petroleum were separated crystals (needles, *ex* light petroleum–ethyl alcohol, m. p. 125—127°) and a syrup from which no definite product could be isolated. No depression of m. p. was observed on mixing the crystalline product with the supposed 3 : 4-diacetyl β-methylglucoside 2 : 6-dinitrate. The syrup (P) did not crystallise and no separation of constituents was effected.

(*d*) In a typical larger-scale repetition of (*c*), 28 g. of starting material gave 5·92 g. of 3 : 4-diacetyl β-methylglucoside 2 : 6-dinitrate and 1·504 g. of β-methylglucoside 3 : 6-dinitrate.

2 : 4-*Dimethyl β-Methylglucoside* 3 : 6-*Dinitrate*.—Methylation of β-methylglucoside 3 : 6-dinitrate (1 g.) gave 1·07 g. of syrup; $n_D^{15°}$ 1·4655, $[\alpha]_D^{15°}$ − 6·9° (chloroform, $l = 2$, $c = 3·50$) (cf. Dewar and Fort, *loc. cit.*).

2 : 4-*Dimethyl β-Methylglucoside*.—Reduction of this dinitrate (0·55 g.) gave a crystalline product (0·39 g.), m. p. 124°, mixed m. p. 124° (cf. Dewar and Fort, *loc. cit.*).

β-Methylglucoside 2 : 6-*Dinitrate*.—3 : 4-Diacetyl β-methylglucoside 2 : 6-dinitrate (6·85 g.) in chloroform (70 c.c.) was treated with methyl alcohol (70 c.c.) in which sodium (0·055 g.) had been dissolved, and the course of the reaction followed polarimetrically. Isolation in the usual way gave the *nitrate* as a syrup (5·048 g.), $n_D^{13°}$ 1·4839, $[\alpha]_D^{13°}$ − 11·6° (chloroform, $l = 2$, $c = 5·03$) (Found: N, 9·7. $C_7H_{13}O_{16}N_3$ requires N, 9·8%).

3 : 4-*Dimethyl β-Methylglucoside* 2 : 6-*Dinitrate*.—The above dinitrate (5 g.) yielded after 2 methylations by Purdie's method a crystalline product (95% yield), which, recrystallised from light petroleum–ethyl alcohol, had m. p. 62—63°, $[\alpha]_D^{13°}$ + 9·7° (chloroform, $l = 2$, $c = 3·707$) (Found: C, 35·1; H, 5·3; N, 8·9. $C_9H_{16}O_{16}N_2$ requires C, 34·6; H, 5·1; N, 8·9%).

3 : 4-*Dimethyl β-Methylglucoside*.—Reduction of the above compound (3·18 g.) in glacial acetic acid (38 c.c.) with zinc and iron powder gave, on isolation in the usual way, a crystalline product (1·967 g.) which was further purified by distillation (b. p. 165—170°/0·9 mm.) and recrystallisation from carbon tetrachloride. It had m. p. 79—81°, unaltered on admixture with 3 : 4-dimethyl β-methylglucoside prepared by another method (Dewar and Fort, *loc. cit.*).

The authors acknowledge their indebtedness to the Carnegie Trust for the grant of a Scholarship, which enabled one of them (G. F.) to take part in the investigation, and to Dr. J. W. H. Oldham (Royal Institution) for his interest and kindly criticism.

THE UNIVERSITY, ST. ANDREWS. [*Received, June 13th*, 1944.]

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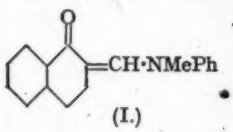
138. *The Direct Introduction of Angular Methyl Groups.*

By ARTHUR J. BIRCH and SIR ROBERT ROBINSON.

2-*Formyl*-1-*decalone* reacts with methylaniline to give 2-*methylanilinomethylene*-1-*decalone* (I), which on succesive treatment with sodamide and methyl iodide, followed by hydrolysis, gives 9-methyl-1-decalone in good yield.

Cook and Lawrence (J., 1937, 823) attempted to introduce an angular methyl group into 1-decalone by treatment of its sodio-derivative with methyl iodide, but obtained mainly 2-methyl-1-decalone, with only a trace of *cis*-9-methyl-1-decalone. Koebner and Robinson (J., 1941, 566), Johnson (*J. Amer. Chem. Soc.*, 1943, **65**, 1317), and Birch (J., 1943, 661) showed that a methylene group adjacent to a carbonyl can be protected by forming the piperonylidene or benzylidene derivative, and an angular alkyl group introduced by direct alkylation. The only process for the removal of the arylidene group is that of Johnson, which is not entirely satisfactory for several reasons, notably because it involves a chlorination.

The methylanilinomethylene derivatives have now been found to be more satisfactory, since this group is readily removed by hydrolysis. *trans*-1-Decalone condensed with ethyl formate in the presence of sodium to give the 2-*formyl* derivative, and this reacted with methylaniline in boiling benzene to give (I). Treatment of this with sodamide in benzene gave a sodio-derivative, which readily reacted with methyl iodide. The product was hydrolysed by boiling with dilute hydrochloric acid to an oil, mainly soluble in dilute sodium hydroxide solution, which must be 2-formyl-9-methyl-1-decalone, since alkaline hydrolysis produced 9-methyl-1-decalone. The overall yield from 1-decalone to 9-methyl-1-decalone was 55%.



(I.)

The product was a mixture of the *cis*- and *trans*-isomers, the former predominating. Although derivatives of both isomers could be prepared from the mixture, no very satisfactory method of separating them has been found. By taking advantage of the differential rates of reaction with semicarbazide, the *trans*-isomeride reacting the more rapidly as already observed by Johnson, it was possible to effect a partial separation.

The process would appear to be generally useful for blocking a methylene group adjacent to a carbonyl, and should facilitate the preparation of other substances containing angular alkyl groups.

Experimental.

2-Formyl-1-decalone.—In the hydrogenation of α-naphthol (100 g.) and alcohol (50 c.c.) with Raney nickel and hydrogen (100—50 atms.) at 145—150°, the addition of 2 c.c. of 20% aqueous sodium hydroxide reduced hydrogenolysis considerably, and 57 g. of a mixture of stereoisomeric 1-decalols were obtained. Oxidation with chromic acid in the usual manner gave *trans*-1-decalone.

trans-1-Decalone (21 g.) and ethyl formate (25 c.c.) were mixed and slowly added to a stirred suspension of powdered sodium (3·5 g.) in dry ether (100 c.c.), with cooling in water. After 12 hours the yellow, semi-solid mass was decomposed with ground ice and water, the red, aqueous layer separated, extracted several times with ether, and acidified with acetic acid. The product was a very pale-yellow, pleasant-smelling oil (19 g.), b. p. 136—138°/11 mm. (Found: C, 73·0; H, 8·9. $C_{11}H_{18}O_2$ requires C, 73·3; H, 8·9%).

2-Methylanilinomethylene-1-decalone.—The above *formyl* compound (19 g.) was mixed with methylaniline (14 g.) in benzene (150 c.c.), and the benzene slowly removed by distillation from a boiling steam-bath over a period of 2 hours, the water produced going over with it. Distillation gave a pale-yellow oil (26·5 g.), b. p. 195—200°/0·3 mm., solidifying to a yellow crystalline solid. A small portion, recrystallised from light petroleum (b. p. 40—60°), had m. p. 84—85° (Found: C, 79·7; H, 8·25. $C_{18}H_{23}ON$ requires C, 80·3; H, 8·5%). On prolonged contact with solvents the crystals disappeared, and a viscous resin was formed, probably owing to the formation of stereoisomers.

Methylation. The methylanilinomethylene compound (26 g.) was dissolved in dry benzene (150 c.c.) and added to dry sodamide formed by the catalytic decomposition of a solution of sodium (2·5 g.) in liquid ammonia (20 c.c.) with a trace of ferric nitrate. After refluxing for 45 minutes the evolution of ammonia ceased, and some solid sodio-derivative separated. Addition of methyl iodide (17 g.) to the cooled solution produced an exothermic reaction, completed by refluxing for 30 minutes. After the solution had been washed with dilute hydrochloric acid, the benzene was removed by distillation, and the residual brownish-yellow resin hydrolysed by boiling for 30 minutes with a large excess of 10% hydrochloric acid. The product was taken up in ether, and extracted with 5% sodium hydroxide. The ether gave on distillation a colourless oil (1·5 g.), b. p. 245—255°, giving derivatives identical with those from the mixture of isomeric 9-methyl-1-decalones described below. Acidification of the alkaline extract with acetic acid gave a colourless oil (13·5 g.), b. p. 136°/8 mm. Hydrolysis of this by refluxing for 45 minutes with 20% sodium hydroxide solution (75 c.c.) gave a colourless camphoraceous oil, (11 g.), b. p. 240—246° (Found: C, 79·6; H, 10·9. Calc. for $C_{11}H_{18}O$: C, 79·5; H, 10·8%).

The semicarbazone, prepared in the usual manner, was a white, crystalline solid, m. p. 198—204°. Repeated crystallisation from methyl alcohol gave eventually a small amount of material, m. p. 226—228°, undepressed by an authentic sample of *cis*-9-methyl-1-decalonesemicarbazone, kindly prepared by Mr. G. F. Beattie by the method of Elliott and Linstead (J., 1938, 660) (Found: C, 64·7; H, 9·2. Calc. for $C_{12}H_{21}ON_3$: C, 64·6; H, 9·4%). Treatment of the semicarbazone with an alcoholic solution of 2 : 4-dinitrophenylhydrazine sulphate gave a 2 : 4-dinitrophenylhydrazone, m. p. 161—162°, undepressed by an authentic sample of *cis*-9-methyl-1-decalone-2 : 4-dinitrophenylhydrazone, m. p. 162—163°.

Preparation of the benzylidene derivative from the mixed ketones and careful crystallisation from alcohol gave the pure *cis*-derivative as pale-yellow prisms, m. p. 103—104° (Found: C, 84·8; H, 8·7. Calc. for $C_{18}H_{22}O$: C, 85·0; H, 8·7%). The more soluble fraction had m. p. 67—72°, and probably consists mainly of the *trans*-compound.

The mixture of ketones gave an orange-yellow 2 : 4-dinitrophenylhydrazone, m. p. 145—150°, which could not be separated into the components by crystallisation, or chromatographic analysis on alumina in a 3 : 1 light petroleum (b. p. 40—60°)–benzene solvent.

To separate the ketones, the mixture was added to an excess of semicarbazide acetate solution, with sufficient alcohol to produce homogeneity, and warmed to 50°, the precipitate being collected as it appeared in four equal portions. After one recrystallisation from alcohol these had the following m. p.'s: (I) 218—219°, (II) 207—209°, (III) 222—224°, (IV) 224—227°. Fraction (I) depressed the m. p. of the *cis*-semicarbazone, and is therefore probably the *trans*-isomeride (Found: C, 64·3; H, 9·4. Calc. for $C_{12}H_{21}ON_3$: C, 64·6; H, 9·4%). Fractions (III) and (IV) were shown by mixed m. p. to be mainly the *cis*-compound.

The authors wish to thank Imperial Chemical Industries Limited, Dyestuffs Division, for financial assistance.

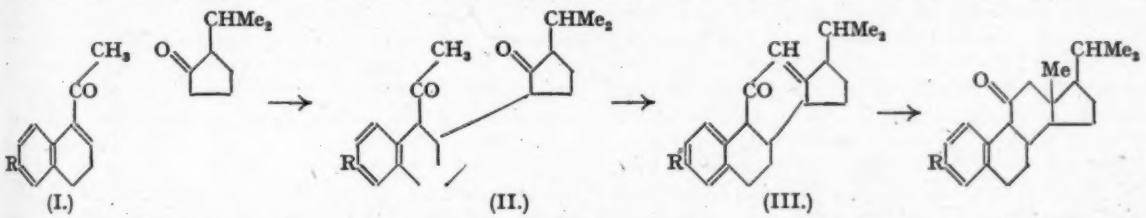
Dyson Perrins Laboratory, Oxford University. [*Received, August 8th*, 1944.]

139. *Experiments on the Synthesis of Substances related to the Sterols. Part XLIII.*

By Arthur J. Birch and Sir Robert Robinson.

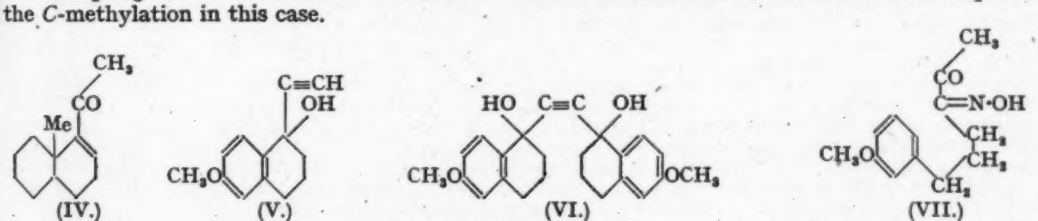
Condensation of (I; R = H, OCH_3) with sodium or lithium 2-*iso*propyl*cyclo*pentanone gives (II; R = H, OCH_3) which may be cyclised by sodium ethoxide, or by heating the sodium or lithium derivative in ether, to (III; R = H, OCH_3), but this does not add methylmagnesium halide to the $\alpha\beta$-double bond in the presence of cuprous halide, the keto-group reacting instead. Compound (IV) is produced by addition of acetylene to 2-keto-9-methyldecalin followed by treatment with mercury acetamide, but fails to add sodium 2-*iso*propyl*cyclo*pentanone.

The construction of the sterol skeleton, ring by ring, must prove very laborious and expensive in materials, so that methods of formation of the complete ring system by locking together two halves are much more attractive. Some progress in this direction has already been made (cf. Peak and Robinson, J., 1937, 1581), but the substances hitherto synthesised lack either angular methyl groups or a substituent at position 17, and introduction of these has proved difficult. The observation (Birch and Robinson, J., 1943, 501) that 2-keto-$\Delta^{1:9}$-octalin can be methylated in the angle group by means of methylmagnesium iodide in the presence of cuprous bromide indicated that the last stage in the type of synthesis outlined below might be possible.

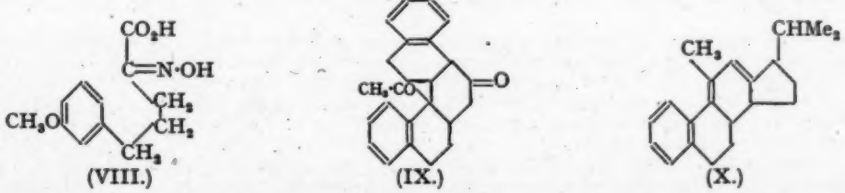


(I.) (II.) (III.)

This, it was hoped, would prove a model for the replacement of (I) by an analogous alicyclic unsaturated ketone which might contain the appropriate angle methyl group and even a second double bond. Further, the side chain of the second component could be that of the sterol, and hence a synthesis of *x*-cholane was envisaged. The preliminary experiments have shown that two of the stages present great difficulty. In the more aromatic series we could not add the angle methyl group and in the alicyclic series we could not bring about the coupling of the two halves. If the latter obstacle could be overcome we do not anticipate trouble with the *C*-methylation in this case.



(IV.) (V.) (VI.) (VII.)



(VIII.) (IX.) (X.)

An attempt was first made to prepare (I; R = OCH_3) from the readily available 1-keto-6-methoxy-1 : 2 : 3 : 4-tetrahydronaphthalene. This has been caused to react with acetylenemagnesium bromide (Dane, Höss, Bindseil, and Schmitt, *Annalen*, 1937, **532**, 39) to give 1-hydroxy-6-methoxy-1-ethynyl-1 : 2 : 3 : 4-tetrahydronaphthalene (V), but when this process was repeated on a larger scale, the main product was always the 1 : 4-diol (VI). The ketone did not react at all with sodium or potassium acetylide or hydrogen cyanide. The small amount of (V) obtained could not be converted into (I; R = OCH_3) by formic acid or by the boron trifluoride–ether complex in various solvents, so the method was abandoned.

We next tried to hydrolyse and cyclise (VII) (obtained by the action of nitrous acid on γ-*m*-methoxyphenylpropylacetoacetic acid) by means of acid reagents, but only a small amount of a compound, probably 1-hydroxy-6-methoxy-1-acetyl-1 : 2 : 3 : 4-tetrahydronaphthalene, was obtained. It was found, however, that 2-*oximino*-5-m-*methoxyphenylvaleric acid* (VIII) (obtained by the action of amyl nitrite on sodium ethyl-γ-*m*-methoxyphenylpropylacetoacetate and hydrolysis) cyclised in good yield by the action of a mixture of concentrated hydrochloric and acetic acids on the steam-bath to 6-*methoxy*-3 : 4-*dihydro*-1-*naphthoic acid*. The acid chloride on treatment with methylzinc iodide gave 6-*methoxy*-1-*acetyl*-3 : 4-*dihydronaphthalene* (I; R = OCH_3). As a

model, condensations with the more readily available 1-acetyl-3 : 4-dihydronaphthalene (obtained by the action of dimethylzinc on 3 : 4-dihydro-1-naphthoyl chloride) were also investigated.

These acetyl-dihydronaphthalenes added sodium or lithium 2-*iso*propyl*cyclo*pentanone (the latter in better yield) to produce the diketones (II; R = OCH_3, H) which underwent ring-closure to (III; R = OCH_3, H) on treatment with alcoholic sodium ethoxide, or by refluxing the sodium or lithium derivatives in ether. The compound (III; R = H) showed the characteristic αβ-unsaturated ketone absorption band in the ultra-violet, $\lambda_{max.}$, 2410 A.; $\varepsilon_{max.}$, 8080. Direct dehydrogenation by means of palladised charcoal gave a crystalline substance which is probably 4-*hydroxy*-3'-iso*propyl*-1 : 2-cyclo*pentenophenanthrene* but reduction by means of sodium in alcohol, followed by treatment with selenium at 320°, gave 3'-*iso*propyl-1 : 2-*cyclo*pentenophenanthrene, the ultra-violet absorption spectrum of which closely resembled that of 1 : 2-*cyclo*pentenophenanthrene itself. The properties of the substance agree with the description by Riegel, Gold, and Kubico (*J. Amer. Chem. Soc.*, 1943, 65, 1772) who have synthesised it since this work was completed. Similarly, reduction of (III; R = OCH_3) followed by selenium dehydrogenation gave 7-*methoxy*-3'-iso*propyl*-1 : 2-cyclo*pentenophenanthrene*. The retention of the *iso*propyl group in these dehydrogenation products proves that addition of the 2-*iso*propyl*cyclo*pentanone has not taken place in the alternative position to give an angular *iso*propyl group on C_1, since this would be eliminated in the dehydrogenation.

In addition to the 4-*keto*-3'-iso*propyl*-1 : 4 : 9 : 10 : 11 : 12-*hexahydro*-1 : 2-cyclo*pentenophenanthrene* (III; R = H), a second substance was isolated from the condensations with (I; R = H) which was evidently the *dimer* of the latter, and by analogy with the results of Jones and Koch (J., 1942, 393) may be formulated as (IX).

By the action of methylmagnesium iodide or bromide in the presence of cuprous bromide or chloride, (III; R = H) gave only a small amount of material extractable by the Girard–Sandulesco reagent P, and this was shown by its ultra-violet absorption spectrum and preparation of the 2 : 4-dinitrophenylhydrazone to be mainly unchanged (III; R = H). It may have been converted by the Grignard reagent into the enol magnesium halide. The main product of the reaction was (X). The compound (III; R = OCH_3) gave no ketonic material extractable by the Girard–Sandulesco reagent P.

In an attempt to arrive at the fully saturated sterol skeleton, the preparation and condensations of (IV) were investigated. 1-Keto-9-methyldecalin reacted readily with sodium acetylide in liquid ammonia to give 1-*hydroxy*-9-*methyl*-1-*ethynyldecalin*, and this gave (IV) by the action of mercury acetamide (cf. Aeschbacher and Goldberg, *Helv. Chim. Acta*, 1939, 22, 1185; Goldberg, Aeschbacher, and Hardegger, *ibid.*, 1943, 26, 680). The unsaturated ketone did not react with sodium 2-*iso*propyl*cyclo*pentanone. The investigation will be continued.

Experimental.

Ethyl γ-m-*Methoxyphenylpropylacetoacetate.*—γ-*m*-Methoxyphenylpropyl iodide (Schlittler and Robinson, J., 1935, 1288) (100 g.) was added to a solution of sodium (12·5 g.) and ethyl acetoacetate (71 g.) in alcohol (150 c.c.). After refluxing for 6 hours, the product was worked up in the usual manner and obtained as a colourless oil (75 g.), b. p. 155—157°/0·2 mm. (Found: C, 69·2; H, 8·4. $C_{16}H_{22}O_4$ requires C, 69·1; H, 8·0%).

3-*Oximino*-2-*keto*-6-m-*methoxyphenylhexane.*—(A) The above ester (10 g.) was refluxed with 4% sodium hydroxide solution (150 c.c.) for 6 hours. 2-Keto-6-*m*-methoxyphenylhexane was obtained as a colourless oil, b. p. 180°/14 mm. Its 2 : 4-dinitrophenylhydrazone crystallised from benzene–alcohol in orange prisms, m. p. 94°. The *semicarbazone* crystallised from alcohol as colourless prisms, m. p. 114° (Found: C, 63·7; H, 7·7. $C_{14}H_{21}O_3N_3$ requires C, 63·8; H, 7·9%). Concentrated hydrochloric acid (4 c.c.) was slowly added to a mixture of the ketone (9 g.) and amyl nitrite (5 g.), cooled in ice. Extraction of the product with an excess of dilute aqueous sodium hydroxide gave a yellow solution, which deposited a yellow oil on acidification. Kept in the refrigerator in contact with light petroleum, this deposited crystals, which recrystallised from light petroleum (b. p. 80—100°) as pearly plates (2·5 g.), m. p. 62°, identical with the substance obtained below.

(B) The above ester (10 g.) was shaken with 2% sodium hydroxide solution (150 c.c.) for 24 hours, most of it then having dissolved. A little oil was removed by ether, and sodium nitrite (2·5 g.) added to the ice-cold solution, which was then acidified. After 8 hours the product was extracted with ether, the ether removed, and the residue extracted with successive portions of boiling light petroleum (b. p. 60—80°) until only a little tar was left. The product crystallised from the solution as colourless, pearly plates (4·5 g.), m. p. 62° (Found: C, 66·5; H, 7·5. $C_{13}H_{17}O_3N$ requires C, 66·4; H, 7·2%).

Attempts to hydrolyse and cyclise this substance to (I; R = OCH_3) with 65% sulphuric acid or a mixture of equal volumes of concentrated hydrochloric and acetic acids on the steam-bath, gave tars. By the latter process a small amount of an oil, b. p. 130°/0·1 mm., was obtained, which gave a dark red 2 : 4-*dinitrophenylhydrazone* (prisms from benzene), m. p. 233° (Found: C, 57·2; H, 4·7. $C_{19}H_{20}O_6N_4$ requires C, 57·0; H, 5·0%). This may be a derivative of 1-hydroxy-6-methoxy-1-acetyl-1 : 2 : 3 : 4-tetrahydronaphthalene.

2-*Oximino*-5-m-*methoxyphenylvaleric Acid.*—Ethyl γ-*m*-methoxyphenylpropylacetoacetate (70 g.) was added to sodium (7 g.) in alcohol (100 c.c.), and the mixture cooled in ice. Amyl nitrite (30 g.) was added in 15 minutes with shaking, the mixture left in cold water for an hour, and then refluxed for 10 minutes. Aqueous sodium hydroxide (200 c.c. of 20%) was added, and refluxing continued for an hour. The mixture was then poured into water (200 c.c.), and the cold solution extracted twice with ether (100 c.c.). It was acidified with dilute sulphuric acid, the oil taken up in ether, and the extract shaken with successive portions of potassium bicarbonate solution until no more acidic material was extracted. Acidification gave a cream-coloured solid (45 g.), a little of which recrystallised from benzene–light petroleum as colourless needles, m. p. 119° (Found: C, 61·0; H, 6·25. $C_{12}H_{15}O_4N$ requires C, 60·7; H, 6·3%).

6-*Methoxy*-3 : 4-*dihydro*-1-*naphthoic Acid.*—The above crude acid (45 g.) was heated on the steam-bath with a mixture of concentrated hydrochloric acid (75 c.c.) and acetic acid (75 c.c.). It passed into solution and crystals began to appear after 15 minutes. After a further 15 minutes the solution was cooled, and water (30 c.c.) added. The solid was crystallised from aqueous acetic acid and obtained as large colourless prisms (31 g.), m. p. 130—131° (Found: C, 70·3; H, 6·0. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%). A little more was recovered by dilution of the mother-liquor. Catalytic reduction of the acid (1 g.) in sodium carbonate solution in the presence of Raney nickel proceeded rapidly, hydrogen (120 c.c.) being absorbed (Calc. for one double bond: 110 c.c.).

The 6-*methoxy*-1 : 2 : 3 : 4-*tetrahydronaphthoic acid* crystallised from ethyl acetate–petroleum (b. p. 60—80°) as colourless flat prisms, m. p. 89° (Found : C, 69·9; H, 6·8. $C_{12}H_{14}O_3$ requires C, 69·8; H, 6·8%).

6-*Methoxy*-1-*acetyl*-3 : 4-*dihydronaphthalene* (I; R = OCH_3).—Phosphorus trichloride (2·5 g.) was added to the above dihydro-acid (7·5 g.) in benzene (150 c.c.), the mixture kept for 2 hours, and then heated to 65° for 90 minutes. The benzene layer was decanted, and the solvent removed under reduced pressure. The product was not distilled, since an attempt to do so at 0·1 mm. resulted in partial decomposition. A small portion treated with aqueous ammonia gave the amide, m. p. 191° (needles from methyl alcohol). The acid chloride (8 g.) in benzene (45 c.c.) was added with stirring and ice-cooling to a solution of methylzinc iodide, prepared from zinc–copper couple and methyl iodide (15 g.), and ethyl acetate (3 g.) in toluene (30 c.c.). After 15 minutes at the room temperature, the mixture was decomposed with ice and dilute hydrochloric acid, and the organic layer refluxed with dilute sodium hydroxide (100 c.c., 10%) for 30 minutes to remove a little ester. The product was obtained as a very pale yellow, viscous oil (4·4 g.), b. p. 200°/16 mm. (Found : C, 76·5; H, 7·2. $C_{13}H_{14}O_2$ requires C, 77·2; H, 7·0%). The *semicarbazone* crystallised from methyl alcohol as colourless prisms, m. p. 120° (Found : C, 64·7; H, 6·8. $C_{14}H_{17}O_2N_3$ requires C, 64·7; H, 6·75%).

1-*Acetyl*-3 : 4-*dihydronaphthalene* (I; R = H).—3 : 4-Dihydro-1-naphthoic acid (28 g.) (Sowinski, *Ber.*, 1891, **24**, 1357) and thionyl chloride (45 c.c.) were refluxed for 20 minutes, excess thionyl chloride removed under reduced pressure and 3 : 4-dihydro-1-naphthoyl chloride distilled as a colourless, pungent oil (28 g.), b. p. 174°/14 mm. A small amount treated with aqueous ammonia gave the amide, m. p. 128° (colourless needles from methyl alcohol). The acid chloride (28 g.) was dissolved in benzene (100 c.c.), cooled in ice, and stirred under nitrogen, and dimethylzinc (7 g.) in benzene (40 c.c.) added during 15 minutes. After a further 15 minutes at room temperature the mixture was decomposed with ice and dilute hydrochloric acid, the benzene removed, and the residue refluxed with 10% sodium hydroxide solution for 15 minutes to remove a little ester. Longer heating with alkali resulted in the formation of notable quantities of the dimer, m. p. 215°, described below. The product was obtained as a colourless, pleasant-smelling oil (17 g.), b. p. 165°/11 mm. (Found : C, 83·6; H, 6·9. $C_{12}H_{12}O$ requires C, 83·7; H, 6·9%). The *semicarbazone* crystallised from methyl alcohol in colourless needles, m. p. 208° (Found : C, 68·75; H, 6·4. $C_{13}H_{15}ON_3$ requires C, 68·2; H, 6·55%), and the 2 : 4-dinitrophenylhydrazone separated from benzene–alcohol in orange-red prisms, m. p. 119—120°.

The ketone (1 g.) was heated with sulphur (0·15 g.) to 220—230° for 2 hours, giving an oil; picrate, m.p. 116°, semicarbazone, m. p. 232°, both undepressed by mixture with the corresponding derivatives of 1-acetylnaphthalene.

Condensation of 1-*Acetyl*-3 : 4-*dihydronaphthalene with* 2-iso*Propyl*cyclo*pentanone*.—(A) 2-*iso*Propyl*cyclo*pentanone (6·5 g.) and powdered sodamide (2·5 g.) were refluxed in ether (40 c.c.) for 7 hours in a current of nitrogen. 1-Acetyl-3 : 4-dihydronaphthalene (10 g.) in ether (30 c.c.) was then slowly added with stirring and ice-cooling. After 12 hours at room temperature, the mixture was refluxed for 30 minutes and then decomposed with ice. After evaporation of a part of the ether, crystals separated and were removed. Extraction of the solid with boiling alcohol left white crystals (3 g.), m. p. 215° (Found : C, 83·3; H, 7·1. $C_{24}H_{24}O_2$ requires C, 83·7; H, 6·9%). The substance was evidently a *dimer* of the acetyl-dihydronaphthalene, probably (IX).

Concentration of the alcoholic extract gave another substance which separated from benzene–light petroleum as white needles (2·5 g.), m. p. 126° (Found : C, 80·5; H, 8·7. $C_{20}H_{26}O_2$ requires C, 80·5; H, 9·0%). The ultra-violet absorption spectrum in alcohol showed a benzene-type band with maxima at 2660 A. and 2645 A., log $\varepsilon_{max.}$ 2·65, and the substance is therefore probably the diketone (II; R = H). It was heated with sodium (0·1 g.) in alcohol (3 c.c.) in an atmosphere of nitrogen on the steam-bath for an hour. The product was a glass, b. p. 193—195°/0·08 mm. (Found : C, 84·3; H, 8·4. $C_{20}H_{24}O$ requires C, 85·7; H, 8·6%). It had probably cyclised, in the main, to (III; R = H). The ethereal solution from the original condensation also gave the same substance on distillation (4 g.), b. p. 198—200°/0·1 mm. (Found : C, 85·2; H, 8·2%).

(B) Lithium (0·7 g.) was converted into the amide by the catalytic action of a trace of ferric nitrate on its solution in liquid ammonia (25 c.c.), the ammonia removed, and dry ether (75 c.c.) added. 2-*iso*Propyl*cyclo*pentanone (12·6 g.) was added with stirring under nitrogen, and the solution refluxed for an hour. 1-Acetyl-3 : 4-dihydronaphthalene (17·2 g.) was then added with stirring and ice-cooling over 15 minutes, the mixture left for 1 hour, and refluxed for 3½ hours. Worked up as above, the crystalline dimer (2·5 g.) was obtained together with (III; R = H) as a glass (16·8 g.), b. p. 193—198°/0·1 mm. (Found : C, 85·4; H, 8·3%). The ultra-violet absorption spectrum showed the typical $\alpha\beta$-unsaturated ketone band at 2410 A.; $\varepsilon_{max.}$, 8080, agreeing fairly closely with the value of 2390 A. given by Woodward (*J. Amer. Chem. Soc.*, 1941, **63**, 1123) for the absorption maximum of a $\beta\beta$-dialkyl $\alpha\beta$-unsaturated ketone. The 2 : 4-*dinitrophenylhydrazone* was obtained as a dark red, amorphous solid, which could not be obtained crystalline, being probably a mixture of *cis*- and *trans*-isomers, but which was purified by passage through a column of alumina in benzene–light petroleum solution. It melted indefinitely at about 85—87° (Found : C, 68·1; H, 6·1; N, 12·7. $C_{28}H_{28}O_4N_4$ requires C, 67·8; H, 6·0; N, 12·2%).

Direct dehydrogenation of the ketone (1 g.) by means of palladised charcoal at 260° for 2 hours gave a solid (0·4 g.) which crystallised from benzene–light petroleum as colourless prisms, m. p. 162° (sintered 158°) (Found : C, 86·8; H, 7·4. $C_{20}H_{20}O$ requires C, 86·9; H, 7·2%). This is probably 4-*hydroxy*-3′-iso*propyl*-1 : 2-cyclo*pentenophenanthrene*, although it was not soluble in dilute aqueous sodium hydroxide. The picrate was obtained as orange needles, m. p. 148—152°.

Reduction of the ketone (1·0 g.) with sodium (5 g.) in alcohol (50 c.c.) and heating the product with selenium (2 g.) to 320° for 5 hours gave an oxygen-free product. This was isolated (crude, m. p. 93°; 450 mg.) by extraction with boiling alcohol, and after several recrystallisations from alcohol, 3′-*iso*propyl-1 : 2-*cyclo*pentenophenanthrene was obtained as colourless plates, m. p. 96° (Found : C, 92·0; H, 7·6. Calc. for $C_{20}H_{20}$: C, 92·3; H, 7·7%). Riegel, Gold, and Kubico (*loc. cit.*) give m. p. 97·6—98·4°. The *picrate* crystallised from alcoholic picric acid as bright yellow needles, m. p. 121° (Found : N, 8·9. $C_{26}H_{23}O_7N_3$ requires N, 8·9%). The 1 : 3 : 5-trinitrobenzene derivative consisted of pale yellow prisms, from alcohol, m. p. 115°.

The ultra-violet absorption spectrum resembled that of 1 : 2-*cyclo*pentenophenanthrene itself, given by Mayneord and Roe (*Proc. Roy. Soc.*, 1935, **152** A, 317). The maxima are compared in the table below, *A* being 3′-*iso*propyl-1 : 2-*cyclo*pentenophenanthrene and *B* 1 : 2-*cyclo*pentenophenanthrene. The main bands are in italics.

A. $\lambda_{max.}$	*3515*	3440	*3355*	3290	*3205*	*3005*	*2890*	*2820*	*2605*		
log $\varepsilon_{max.}$	2·98	2·52	2·88	2·58	2·76	4·06	3·98	3·98	4·74		
B. $\lambda_{max.}$	*3520*	3440	*3360*	3290	*3210*	3140	*3005*	*2880*	*2800*	*2570*	*2150*
log $\varepsilon_{max.}$	2·99	2·55	2·99	2·54	2·74	2·55	4·22	4·10	4·16	4·80	4·50

Condensations of 6-*Methoxy*-1-*acetyl*-3 : 4-*dihydronaphthalene and* 2-iso*Propyl*cyclo*pentanone*.—2-*iso*Propyl*cyclo*pentanone (2·8 g.) and lithium amide (from lithium, 0·18 g.) were refluxed in dry ether (15 c.c.) for 1½ hours, the solution cooled in ice, and 6-methoxy-1-acetyl-3 : 4-dihydronaphthalene (4·4 g.) in ether (15 c.c.) slowly added with stirring under nitrogen. After refluxing for 3 hours, dry alcohol (15 c.c.) was added, and refluxing continued for 1 hour. Addition of dilute hydrochloric acid, extraction with ether and distillation gave the product as a glass (3·8 g.), b. p. 220—

235°/0·1 mm. Redistillation gave a pale yellow glass (3·1 g.), b. p. 128—134°/0·15 mm. (Found: C, 80·3; H, 8·2. $C_{21}H_{26}O_2$ requires C, 81·3; H, 8·4%). That this was mainly 4-*keto*-7-*methoxy*-3′-*isopropyl*-1 : 4 : 9 : 10 : 11 : 12-*hexahydro*-1 : 2-cyclo*pentenophenanthrene* was shown by dehydrogenation. The substance (1 g.) was reduced with sodium (1 g.) and alcohol (10 c.c.), and the product heated with selenium (2 g.) to 320—330° for 5 hours. Extraction with boiling alcohol gave the product as pearly plates (230 mg.). It was purified by passage through alumina in benzene solution, and crystallised from alcohol as colourless plates, m.p. 129° (Found: C, 86·0; H, 7·5. $C_{21}H_{22}O$ requires C, 86·8; H, 7·6%). Alcoholic picric acid gave the picrate as bright orange needles, m. p. 156°.

The ketone gave no crystalline derivative with semicarbazide or 2 : 4-dinitrophenylhydrazine.

If the refluxing in the original condensation was omitted, a considerable proportion of a crystalline solid was obtained. This crystallised from alcohol as colourless needles, m. p. 171—173° (Found: C, 76·6; H, 8·7. $C_{21}H_{28}O_3$ requires C, 76·8; H, 8·6%). It was therefore 6-*methoxy*-2-(3′-*isopropyl*cyclo*pentan*-2′-*onyl*)-1-*acetyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (II; R = OCH_3).

Reactions with Grignard Reagents.—Keto*iso*propylhexahydro*cyclo*pentenophenanthrene (2 g.) in dry ether (20 c.c.) was added slowly with stirring and cooling under nitrogen to a Grignard solution from magnesium (0·2 g.) and methyl iodide (1 g.) in ether (10 c.c.) with addition of cuprous bromide (0·05 g.). A further 0·05 g. was added half-way through the mixing. After decomposition in the usual manner, the product was separated by the Girard–Sandulesco reagent P into a ketonic and a non-ketonic fraction. The latter was heated to 180° with a trace of iodine, a little water being evolved. Distillation gave a colourless oil (1·4 g.), b. p. 190°/0·1 mm. (Found: C, 90·3; H, 9·7. $C_{21}H_{34}$ requires C, 90·6; H, 9·4%). It was, therefore, 4-*methyl*-3-*isopropyl*-1 : 9 : 10 : 11-*tetrahydro*-1 : 2-cyclo*pentenophenanthrene* (X). The ketonic fraction distilled as a glass (0·3 g.), b. p. 190—195°/0·1 mm. (Found: C, 85·1; H, 9·0. $C_{20}H_{34}O$ requires C, 85·7; H, 8·6%. $C_{21}H_{28}O$ requires C, 85·1; H, 9·5%). The ultra-violet absorption spectrum still showed the $\alpha\beta$-unsaturated ketone band at 2390 A., although $\varepsilon_{max.}$ was lower at about 5000. It gave a 2 : 4-dinitrophenylhydrazone as a red amorphous solid, m. p. *ca.* 85° (Found: C, 67·4; H, 6·3. Calc. for $C_{26}H_{32}O_4N_4$: C, 67·8; H, 6·0%). It therefore corresponded to starting material, from the 2 : 4-dinitrophenylhydrazone of which it could not be separated by chromatographing in benzene–light petroleum on alumina.

The analysis and the low value of $\varepsilon_{max.}$ probably indicate the presence of a little of the desired product.

Repetition of the Grignard addition under varying conditions, using methylmagnesium bromide and cuprous chloride, gave essentially the same results. In the case of ketomethoxy*iso*propylhexahydro*cyclo*pentenophenanthrene the Grignard additions did not give any ketonic substance extractable by the Girard–Sandulesco reagent P.

The following experiments were made in collaboration with Mr. G. F. Beattie.

1-*Hydroxy*-9-*methyl*-1-*ethynyldecalin*.—A mixture of *cis*- and *trans*-1-keto-9-methyldecalin (8·3 g.) (obtained by the method of Birch and Robinson) (cf. preceding paper) in ether (15 c.c.) was slowly added to a liquid ammonia solution of sodium acetylide, from sodium (1·3 g.) in liquid ammonia (50 c.c.), in a 150 c.c. Dewar flask. Acetylene was bubbled through the mixture for 3 hours and it was then left for 12 hours. After decomposition with ice the product was taken up in ether, dried and distilled. It was a colourless, camphoraceous oil (8 g.), b. p. 130—132°/9 mm. (Found: C, 81·1; H, 10·8. $C_{13}H_{20}O$ requires C, 81·2; H, 10·5%).

1-*Acetyl*-9-*methyl*-Δ^1-*octalin*.—Attempts to produce this substance from the above ethynylcarbinol by the action of formic acid or boron trifluoride–ether in acetic acid or alcohol did not give the required product. It was obtained as follows. The ethynylcarbinol (19 g.) and mercury acetamide (58 g.) were refluxed in absolute alcohol (140 c.c.) for 3 hours. After saturation with hydrogen sulphide, the mercuric sulphide was coagulated by the addition of a few drops of concentrated hydrochloric acid and removed by centrifuging. Distillation gave a colourless oil (11 g.), b. p. 110—140°/9 mm. This was warmed on the steam-bath with an excess of aqueous-alcoholic semicarbazide acetate for 15 minutes, giving a colourless semicarbazone, m. p. 200—205°, undepressed by the semicarbazone of the original 1-keto-9-methyldecalin. On refluxing with 10% hydrochloric acid it gave this ketone as a colourless, camphoraceous oil (4 g.), b. p. 110—112°/9 mm. The mother-liquor from the semicarbazide was diluted with water, extracted with ether and distilled, giving fractions, b. p. 120—128°/9 mm. (2 g.), 135—137°/9 mm. (4 g.). The latter fraction was the required substance (Found: C, 81·3; H, 10·9. $C_{13}H_{20}O$ requires C, 81·2; H, 10·5%). It showed the $\alpha\beta$-dialkyl $\alpha\beta$-unsaturated ketone band in the ultra-violet at $\lambda_{max.}$ 2370 A.; $\varepsilon_{max.}$ 7690. On treatment with 2 : 4-dinitrophenylhydrazine sulphate in alcohol it gave a solid 2 : 4-*dinitrophenylhydrazone* in 93% yield, crystallising as bright orange prisms from benzene–alcohol, m. p. 143—146° (Found: C, 60·9; H, 6·5. $C_{19}H_{24}O_4N_4$ requires C, 61·3; H, 6·5%). A sample of the pure cis-2 : 4-*dinitrophenylhydrazone*, prepared in the same manner from *cis*-1-keto-9-methyldecalin made by the method of Elliott and Linstead (J., 1938, 662), had m. p. 169° (Found: C, 60·9; H, 6·4. $C_{19}H_{24}O_4N_4$ requires C, 61·3; H, 6·5%).

The ketone failed to condense with sodium 2-*iso*propyl*cyclo*pentanone in ether or boiling benzene.

Absorption spectra are by Dr. F. B. Strauss.

The authors are grateful to Imperial Chemical Industries Limited, Dyestuffs Division, for grants which have enabled this investigation to be made.

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, August 8th*, 1944.]

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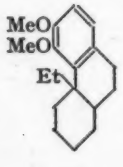
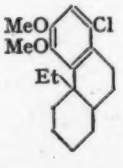
140. *Synthesis of Substances possibly obtainable as Degradation Products of Thebaine.*

By R. GHOSH and SIR ROBERT ROBINSON.

3 : 4-Dimethoxy-13-ethyl-5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-octahydrophenanthrene (I) and its 1-*chloro*-derivative (II) could probably be obtained from thebaine (III) by a series of processes.



(I.)



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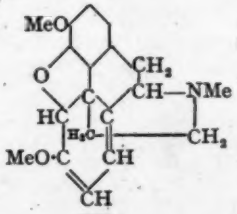
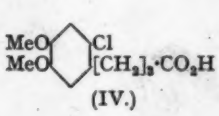


(III.)

Syntheses of both (I) and (II) in undetermined stereo-configuration are described. Ketonic intermediates have been characterised and may also be of interest in relation to the morphine–thebaine chemistry.

γ-3 : 4-DIMETHOXYPHENYLBUTYRIC acid (Haworth and Mavin, J., 1932, 1486) was chlorinated to γ-2-*chloro*-4 : 5-*dimethoxyphenylbutyric* acid (IV) with the object of directing the subsequent ring-closure into position 6. Difficulty was encountered in this cyclisation, and various methods, such as treatment of the acid with sulphuric acid, phosphoric anhydride in benzene, or phosphoryl oxychloride, proved to be unsatisfactory. Treatment of the acid chloride with aluminium chloride was also unsatisfactory. The yield of the ketone, 1-*chloro*-5-*keto*-3 : 4-*dimethoxy*-5 : 6 : 7 : 8-*tetrahydronaphthalene* (V), was very unfavourable and the product was always accompanied by varying amounts of 1-*chloro*-5-*keto*-4-*hydroxy*-3-*methoxy*-5 : 6 : 7 : 8-*tetrahydronaphthalene* (VI). Stannic chloride was then used to bring about the ring-closure of the acid chloride under various conditions and finally the ketone (V) was thus obtained in 80—90% yield, although accompanied by a trace of (VI), which could, however, be methylated to (V) by means of methyl sulphate and alkali. The next stage, a Grignard reaction with ethylmagnesium bromide and the ketone (V), was tried under various conditions and an 80—90% yield of the product was realised when one molecule of the ketone was treated with 4—5 molecules of ethylmagnesium bromide in ether. The product proved to be a mixture of 1-chloro-5-hydroxy-3 : 4-dimethoxy-5-ethyl-5 : 6 : 7 : 8-tetrahydronaphthalene and 1-*chloro*-3 : 4-*dimethoxy*-5-*ethyl*-7 : 8-*dihydronaphthalene* (VII). The mixture was successfully dehydrated in good yield by distillation over phosphoric anhydride in a vacuum. Other methods, such as the use of the same reagent in boiling benzene or dehydration in presence of thionyl chloride and pyridine, formic acid, oxalic acid, and iodine, were tried, but none proved suitable. The dihydronaphthalene (VII) was then subjected to oxidation with (i) mercuric acetate, (ii) perbenzoic acid, (iii) hydrogen peroxide in acetic acid. In the first case a product was isolated, after the usual treatment with 10% sulphuric acid, which gave the same analysis as the desired β-tetralone derivative, but was devoid of ketonic properties and was probably the *oxide* (VIII). Treatment of (VII) with perbenzoic acid, followed by isomerisation of the resulting oxide to the ketone (IX), gave a very poor yield. Oxidation of (VII) with hydrogen peroxide in acetic acid gave more promising results, and the yield of the *ketone* (IX) so far attained is 33%. (IX) was then condensed with the methiodide of β-diethylaminoethyl methyl ketone in presence of sodamide, and the resulting product proved to be 1-*chloro*-7-*keto*-3 : 4-*dimethoxy*-13-*ethyl*-5 : 6 : 7 : 9 : 10 : 13-*hexahydrophenanthrene* (X), having the properties of an αβ-unsaturated ketone and giving a scarlet-red 2 : 4-*dinitrophenylhydrazone*. Reduction of (X) in presence of palladium–charcoal in alcohol gave 1-*chloro*-7-*keto*-3 : 4-*dimethoxy*-13-*ethyl*-5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-*octahydrophenanthrene* (XI), which was reduced to (II) by Clemmensen's method. As a result of the catalytic reduction, (XI) was accompanied by a small amount of 7-*keto*-3 : 4-*dimethoxy*-13-*ethyl*-5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-*octahydrophenanthrene* (XII), and consequently (II) by a small amount of (I).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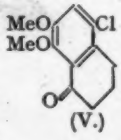
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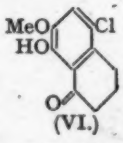
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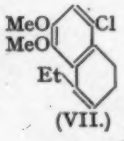
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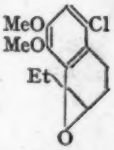
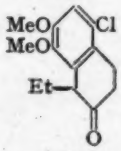

(VIII.)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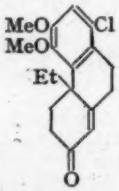
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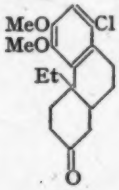
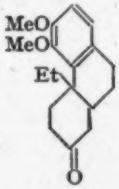
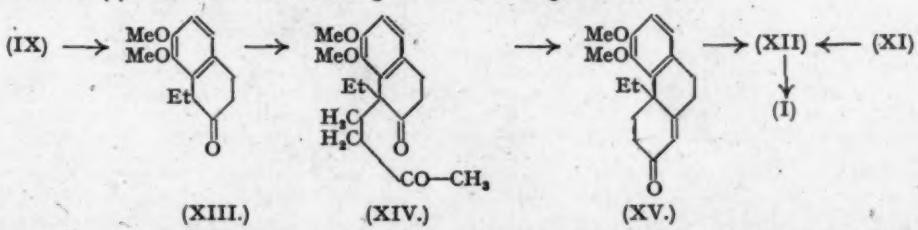

(XI.)


(XII.)

The product (II) proved to be a colourless viscous liquid, readily soluble in organic solvents. In the hope of obtaining the pure *cis*-modification, (X) was reduced in the presence of platinic oxide (cf. Ruzicka, Brüngger, Eichenberger, and Meyer, *Helv. Chim. Acta*, 1934, 17, 1407), and the product further reduced by amalgamated zinc and hydrochloric acid. It was still an oil and could not be induced to crystallise.

The synthesis of (I) was achieved according to the following scheme :



(XIII.) (XIV.) (XV.)

Thus (IX) was dehalogenated to (XIII), and the latter condensed with the methiodide of 4-diethylaminobutan-2-one. The results of the condensation depended on the amount of sodamide used; in presence of a small

quantity of the reagent the product was mainly (XIV), while a large excess gave (XV), slightly contaminated with (XIV). Reduction of (XV) with hydrogen in the presence of platinic oxide, in alcohol, gave (XII), which was also obtained by dehalogenating (XI). Clemmensen reduction of (XII) gave (I) as a colourless, thick liquid, soluble in all organic solvents. Attempts to crystallise this substance have not yet been successful. It may be mentioned that dehalogenation of (II) to (I) could not be accomplished.

Further work on the preparation of crystalline derivatives of (I) is in progress and when oppportunity offers the conversion of thebaine into (I) will be attempted.

Experimental.

γ-3 : 4-Dimethoxyphenylbutyric Acid.—The method of Haworth and Mavin (*loc. cit.*) was slightly modified. Succinic anhydride (44 g.) and veratrole (64 g.) were added to a solution of aluminium chloride (120 g.) in nitrobenzene (400 c.c.), and the mass stirred mechanically with cooling in running water. After 24 hours it was decomposed with ice and hydrochloric acid, and steam-distilled. After removal of nitrobenzene and cooling, the solid was collected and dissolved in boiling sodium carbonate solution (charcoal). Acidification of the filtered solution gave veratroylpropionic acid, m. p. 159—161° (Haworth and Mavin, 160—161°). This was refluxed for 15 hours with amalgamated zinc (280 g.), and concentrated hydrochloric acid, replenished from time to time (1500 c.c. in all). The cooled mixture was extracted with chloroform, the extract washed with water, and the solvent removed. The residue was treated with aqueous sodium bicarbonate, and the solution washed with ether. It was then acidified, the acid isolated by means of chloroform, and distilled under 0·2 mm. The distillate solidified to a snow-white mass, and on crystallisation from chloroform–light petroleum (b. p. 60—80°) afforded colourless prisms, m. p. 58—59° (Haworth and Mavin, m. p. 57—59°) (yield, 70—80%).

γ-2-Chloro-4 : 5-dimethoxyphenylbutyric Acid (IV).—A solution of veratrylbutyric acid (75 g.) in glacial acetic acid (200 c.c.) was cooled to 10—15° and dry chlorine (from 27 g. of potassium permanganate), diluted with air, passed in with vigorous stirring. After 2 hours the mixture was slowly heated, and finally boiled for 5 minutes. It was then cooled and poured into ice-water, whereupon a mixture of the *chloro-acid* and unchanged material separated. This was triturated with cold ether, in which the chloro-acid was sparingly soluble, and the residue was twice crystallised from large volumes of ether (charcoal). Colourless, prismatic needles, m. p. 112°, were obtained (yield, 70%) (Found: C, 55·8; H, 5·7; equiv., 259. $C_{12}H_{15}O_4Cl$ requires C, 55·7; H, 5·8%; equiv., 258·5).

1-Chloro-4-hydroxy-5-keto-3-methoxy-5 : 6 : 7 : 8-tetrahydronaphthalene (VI).—Chlorodimethoxyphenylbutyric acid (6·0 g.) was mixed with sulphuric acid (8 c.c. of 80%) and warmed on the steam-bath for ½ hour. After addition to ice, an ether extract was washed with sodium bicarbonate solution, water, and dried. The yellowish product crystallised from methanol as pale yellow needles, m. p. 104—105° (yield, 2·0 g.) (Found: C, 57·5; H, 4·8. $C_{11}H_{11}O_3Cl$ requires C, 58·3; H, 4·9%). The *chloro-ketone* gives a greenish-yellow solution in dilute aqueous sodium hydroxide. The *oxime* (pyridine method) crystallised from methanol in colourless needles, m. p. 205—206° (Found: N, 6·0. $C_{11}H_{12}O_3NCl$ requires N, 5·8%). The 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid as orange needles which decomposed above 286° (Found: N, 13·8. $C_{17}H_{15}O_6N_4Cl$ requires N, 13·8%).

1-Chloro-5-keto-3 : 4-dimethoxy-5 : 6 : 7 : 8-tetrahydronaphthalene (V).—(A) Chlorodimethoxyphenylbutyric acid (5 g.) was dissolved in benzene (60 c.c.), and phosphoric anhydride (20 g.) added in small portions during 3 hours. After cooling, the benzene was decanted, and the residue decomposed with ice and extracted with ether. The ethereal extract and the benzene solution were combined, washed with dilute aqueous sodium hydroxide and water, dried over potassium carbonate and the solvent removed. The residue was distilled from a bath at 134—140°/0·02 mm., and the distillate, which soon solidified, crystallised from alcohol as colourless needles, m. p. 77·5—78° (yield, 0·8 g.) (Found: C, 60·2; H, 5·4; Cl, 15·0. $C_{12}H_{13}O_3Cl$ requires C, 59·9; H, 5·4; Cl, 14·8%). On acidification of the above alkaline washings, and extraction with ether and removal of acidic materials with sodium bicarbonate solution, 1-chloro-4-hydroxy-5-keto-3-methoxy-5 : 6 : 7 : 8-tetrahydronaphthalene was obtained, m. p. 104—105° after crystallisation (0·3 g.).

The 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid as red needles, m. p. 242—243° (Found: N, 13·5. $C_{18}H_{17}O_6N_4Cl$ requires N, 13·3%). The *semicarbazone* crystallised from alcohol in colourless, silky plates, m. p. 218° (Found: C, 52·5; H, 5·2; N, 13·9. $C_{13}H_{16}O_3N_3Cl$ requires C, 52·4; H, 5·4; N, 14·1%).

(B) γ-2-Chloro-4 : 5-dimethoxyphenylbutyric acid (10 g.) was boiled for 5 minutes with phosphoryl chloride (30 c.c.), then poured into ice-water, and the mixture extracted with ether and worked up as above. The alkali-insoluble ketone (0·5 g.) and the alkali-soluble ketone (1·6 g.) had the properties already described. Mixed m. p.'s with authentic samples were not depressed.

(C) Chlorodimethoxyphenylbutyric acid (5 g.) was dissolved in benzene (35 c.c.) at 50°, and powdered phosphorus pentachloride (6 g.) gradually added. The acid chloride was formed with evolution of hydrogen chloride and the mixture was kept at 40—50° for 2 hours. After cooling to 0°, stannic chloride (6 c.c.) was added with shaking and the temperature maintained for 36 hours. The mixture was then poured into concentrated hydrochloric acid (30 c.c.), ether (30 c.c.) and ice, with stirring. The layers were separated, and the aqueous solution extracted with 6 portions of ether (150 c.c.). The combined extracts were then washed with hydrochloric acid, sodium hydroxide solution, and water and dried. The residue after removal of the solvent was purified as already described. M. p. and mixed m. p. with an authentic sample of 1-chloro-5-keto-3 : 4-dimethoxy-5 : 6 : 7 : 8-tetrahydronaphthalene were 77·5—78° (yield 85—90%).

From the alkali washings the partly demethylated ketone was obtained in the usual way; m. p. and mixed m. p. with an authentic sample, 104—105°. Only a very small quantity of this phenolic substance was isolated.

(D) The above phenolic ketone (VI) (5 g.) was dissolved in methanol (70 c.c.), and methyl sulphate (12 c.c.) and methanolic potassium hydroxide (15 g. in 80 c.c.) gradually added with refluxing on the steam-bath. After 4 hours, most of the methanol was distilled, and the residue was cooled and extracted with chloroform. The chloroform extract was washed with water, dried, and evaporated. The residue was distilled under reduced pressure and crystallised as mentioned above; m. p. 78°, alone or mixed with an authentic sample.

1-Chloro-3 : 4-dimethoxy-5-ethyl-7 : 8-dihydronaphthalene (VII).—A solution of chlorodimethoxytetralone (6·0 g.) in ether (190 c.c.) was slowly added to one of ethylmagnesium bromide (from 3 g. of magnesium, 10 c.c. of ethyl bromide, and 50 c.c. of ether), and the mixture kept for 48 hours at the room temperature. It was then refluxed for 2 hours, cooled and decomposed with ice and hydrochloric acid, and the ethereal layer separated. The aqueous solution was further extracted with ether, and the combined extracts were washed with water, dilute alkali, water, and dried. The solvent was removed and the residue distilled at 0·1—0·2 mm. The distillate (6·0 g.), which contained some carbinol, was dissolved in ether (20 c.c.), and the solution treated with phosphoric anhydride (6·0 g.). Ether was then removed and the residue slowly distilled at <0·1 mm.

In redistillation the *chloro-compound* was collected at 110° (bath temp.)/0·02 mm. as a colourless, sweet-smelling liquid (yield, 5·0—5·5 g.) (Found: C, 67·1; H, 6·6. $C_{14}H_{17}O_2Cl$ requires C, 66·5; H, 6·7%).

Oxidation of 1-Chloro-3 : 4-dimethoxy-5-ethyl-7 : 8-dihydronaphthalene with Mercuric Acetate.—Chlorodimethoxy-

ethyldihydronaphthalene (2·5 g.) was added to a solution of mercuric acetate (6·4 g.) in acetic acid (80 c.c.) and water (20 c.c.), and the mixture heated on the steam-bath. Very soon mercurous acetate began to separate in shining plates. Heating was continued for 1 hour, the mixture was then cooled and filtered, and the residue washed with acetic acid. The filtrate and washings were combined and the solvent removed under reduced pressure. The residue was refluxed with dilute sulphuric acid (50 c.c., 15%) for 3 hours, cooled and extracted with ether in the usual way. After removal of ether, the residue was distilled and a fraction (0·8 g.), b. p. 125—140° (bath temp.)/0·02 mm., was collected. This was treated with alcohol (15·0 c.c.), Girard reagent T (1·0 g.) and acetic acid (2·2 g.), refluxed for 2 hours, then cooled and poured into a cold solution of sodium carbonate (1·7 g.) in water (50 c.c.). The mixture was extracted with ether and the non-ketonic part so separated. The aqueous solution was acidified with hydrochloric acid and warmed for 2 hours in the steam-bath, cooled and extracted with ether; on removal of ether a very small residue was obtained and was not further investigated. The non-ketonic material (? VIII) was distilled and collected as a pale yellow viscous oil, b. p. 135° (bath temp.)/0·02 mm. (Found: C, 62·8; H, 6·3. $C_{14}H_{17}O_3Cl$ requires C, 62·6; H, 6·3%).

1-*Chloro*-6-*keto*-3 : 4-*dimethoxy*-5-*ethyl*-5 : 6 : 7 : 8-*tetrahydronaphthalene* (IX).—(A) Chlorodimethoxyethyldihydronaphthalene (5·3 g.) was dissolved in acetic acid (40 c.c.) and perhydrol (4 c.c. of 30%) added. The clear solution was kept at room temperature for 4 days, and then most of the acetic acid was removed under reduced pressure and the residue refluxed with dilute sulphuric acid (14 c.c., *d* 1·84, in 100 c.c. of water) for 7 hours. It was then cooled, extracted with ether, the ethereal extract washed with water and sodium bicarbonate solution, and dried. The residue, after removal of ether, was distilled and a fraction, collected at 120—150° (bath temp.)/0·01 mm., was dissolved in alcohol and treated with a saturated aqueous solution of semicarbazide hydrochloride (2 g.) and sodium acetate (5·0 g.). Just enough alcohol was then added to give a clear solution. It was then warmed for 5 minutes and left at room temperature for 12 hours. The crystalline precipitate was collected, washed with alcohol, water, alcohol, and crystallised from a large volume of alcohol; colourless needles, m. p. 219—220° (yield, 33%) (Found: C, 55·0; H, 6·2; N, 12·5. $C_{15}H_{20}O_3N_3Cl$ requires C, 55·3; H, 6·1; N, 12·9%). The *semicarbazone* (0·4 g.) was refluxed with dilute sulphuric acid (5·6 c.c., *d* 1·84, in 30 c.c. of water) for 1½ hours, cooled and extracted with ether. The residue after removal of solvent distilled as a colourless oil, b. p. 136—140° (bath temp.)/0·01 mm., which soon solidified (yield, 0·32 g.). This was crystallised from ether–light petroleum (b. p. 40—60°) and colourless prisms, m. p. 66·5—67°, were obtained (Found: C, 62·9; H, 6·4; Cl, 13·4. $C_{14}H_{17}O_3Cl$ requires C, 62·6; H, 6·3; Cl, 13·2%). The *ketone* does not give the iodoform test.

The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol as orange, microscopic needles, m. p. 140° (Found: C, 54·2; H, 4·7; Cl, 12·7. $C_{20}H_{21}O_6N_4Cl$ requires C, 53·6; H, 4·7; Cl, 12·5%).

(B) Chlorodimethoxyethyldihydronaphthalene (2·6 g.) in chloroform (10 c.c.) was treated with perbenzoic acid (1·5 g. in 28 c.c. of chloroform) and the solution kept at 0° for 5 days. More chloroform was then added, and after being washed several times with 10% sodium hydroxide solution, the chloroform layer was dried. After removal of solvent, the residue was distilled and a colourless viscous liquid (2·4 g.), b. p. 130—150° (bath temp.)/0·01 mm., was obtained. This was dissolved in light petroleum (b. p. 60—80°, 50 c.c.), and dry hydrogen chloride passed in for 1½ hours. Ice-cold water was then added and the mixture extracted several times with ether, the ether–petroleum extract washed with water, sodium bicarbonate solution, and dried. After removal of the solvent, the residue was distilled under reduced pressure, and the distillate treated with semicarbazide hydrochloride and sodium acetate as in the previous experiment. A precipitate (0·098 g.) was obtained, which crystallised from alcohol in colourless needles, m. p. 219—220°, alone or mixed with an authentic sample.

1-*Chloro*-7-*keto*-3 : 4-*dimethoxy*-13-*ethyl*-5 : 6 : 7 : 9 : 10 : 13-*hexahydrophenanthrene* (X).—The above ethylated ketone (0·84 g.) was dissolved in dry ether (15·0 c.c.), and finely powdered sodamide (0·3 g.) added under nitrogen. Dry ether was added from time to time to maintain the original volume. After 6 hours an alcoholic solution (10 c.c.) of the methiodide of 4-diethylaminobutan-2-one (from 0·6 g. of the base) was added, and the whole kept at the room temperature for 12 hours in an atmosphere of nitrogen. It was then refluxed for 1½ hours, cooled, and poured into an ice-cold, dilute hydrochloric acid, the mixture extracted with ether, and the extracts washed with water, dilute aqueous sodium hydroxide and water. After drying over anhydrous sodium sulphate, the solvent was removed, and the residue distilled. A fraction, b. p. 180—200° (bath temp.)/0·02 mm., was collected and redistilled. The product was obtained as a pale yellow glass, b. p. 175—180° (bath temp.)/0·005 mm. (Found: C, 67·6; H, 6·5%). The *chloro-ketone* crystallised from methanol in colourless prisms, m. p. 149—149·5° (Found: C, 67·1; H, 6·6; Cl, 11·1. $C_{18}H_{21}O_3Cl$ requires C, 67·4; H, 6·6; Cl, 11·4%). The 2 : 4-*dinitrophenylhydrazone* was obtained as scarlet-red plates, m. p. 206—207°, after crystallisation from alcohol (Found: C, 57·5; H, 4·8. $C_{24}H_{25}O_6N_4Cl$ requires C, 57·5; H, 5·0%).

1-*Chloro*-7-*keto*-3 : 4-*dimethoxy*-13-*ethyl*-5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-*octahydrophenanthrene* (XI).—(A) The above ketone (X) (0·296 g.) in alcohol (30 c.c.) was hydrogenated in the presence of palladised charcoal; 20·4 c.c. of hydrogen were absorbed (calc., 20 c.c.). The concentrate from the filtered solution was refluxed for 8 hours with amalgamated zinc (10·0 g.) and concentrated hydrochloric acid, the latter being added in small quantities (total, 50·0 c.c.). The product was isolated by means of ether and was a colourless, viscous oil, b. p. 152—155° (bath temp.)/0·16 mm. (Found: C, 70·4; H, 8·0; Cl, 11·8. $C_{18}H_{25}O_3Cl$ requires C, 70·0; H, 8·1; Cl, 11·5%). It is insoluble in water but soluble in organic solvents. It does not decolourise permanganate solution. Attempts to crystallise it have not been successful.

(B) The ketone (0·25 g.) was dissolved in alcohol (30 c.c.) and reduced with hydrogen in the presence of platinic oxide (Adams's catalyst). The reduction was over in 1½ hours, the theoretical volume of hydrogen being absorbed. The filtrate, on concentration and cooling, afforded crystals, m. p. 95—100°, and on recrystallisation from alcohol 1-*chloro*-7-*keto*-3 : 4-*dimethoxy*-13-*ethyl*-5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-*octahydrophenanthrene* (XI) was obtained as colourless cubes, m. p. 99—100° (Found: C, 67·01; H, 6·97. $C_{18}H_{23}O_3Cl$ requires C, 66·97; H, 7·13%).

This reduced ketone (XI) (0·073 g.) was refluxed for 5 hours with amalgamated zinc (10 g.) and hydrochloric acid, the acid being added in small quantities (total, 70 c.c.), and worked up as before. The product distilled as a colourless viscous oil at 140—143° (bath temp.)/0·06 mm. (Found: C, 70·3; H, 8·1; Cl, 12·1. $C_{18}H_{25}O_3Cl$ requires C, 70·0; H, 8·1; Cl, 11·5%).

7-*Keto*-3 : 4-*dimethoxy*-13-*ethyl*-5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-*octahydrophenanthrene* (XII).—The ketone (XI; m. p. 99—100°; 0·3 g.) in alcohol (50 c.c.) was mixed with palladised calcium carbonate (cf. Busch and Stöve, *Ber.*, 1916, **49**, 1063) (1·5 g.) and alcoholic potassium hydroxide (0·4 g. in 5 c.c.) and shaken in an atmosphere of hydrogen. After 3 hours the solution was filtered from the catalyst, acetic acid (5 c.c.) added, and the solvent removed under reduced pressure. The product was isolated by means of ether and distilled at 155—160° (bath temp.)/0·02 mm. The ketone in the distillate was converted into its *semicarbazone*, which crystallised from alcohol in colourless, microscopic prisms, m. p. 198·5° (Found: C, 65·8; H, 7·6; N, 12·2. $C_{19}H_{27}O_3N_3$ requires C, 66·1; H, 7·8; N, 12·2%). The *ketone* regenerated from this derivative by means of boiling dilute sulphuric acid (10%) was collected at 158° (bath temp.)/0·03 mm. as a colourless viscous oil (Found: C, 75·5; H, 8·9. $C_{18}H_{24}O_3$ requires C, 75·0; H, 8·3%).

3 : 4-*Dimethoxy*-13-*ethyl*-5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-*octahydrophenanthrene* (I).—The above ketone (XII) (0·35 g.) was refluxed with amalgamated zinc (10·0 g.) and hydrochloric acid (56 c.c.) for 5 hours, and the product isolated by extraction with ether in the usual way. After removal of solvent, the residue was distilled as a colourless viscous oil,

at 110—112° (bath temp.)/0·09 mm. (Found: C, 79·3; H, 9·2. $C_{18}H_{26}O_2$ requires C, 78·8; H, 9·5%). I: does not decolourise permanganate solution.

6-*Keto*-3 : 4-*dimethoxy*-5-*ethyl*-5 : 6 : 7 : 8-*tetrahydronaphthalene* (XIII).—The chloro-ketone (IX) (0·27 g.) was dissolved in alcohol (50 c.c.), palladised strontium carbonate (1·5 g.) and alcoholic potassium hydroxide (5 c.c. of 10%) added, and the mixture shaken with hydrogen. After 2½ hours, it was acidified with acetic acid (4 c.c.), filtered, and the filtrate evaporated to dryness. The residue was treated with water and extracted with ether in the usual was. After removal of solvent the residue was distilled, and a colourless liquid, b. p. 114° (bath temp.)/0·03 mm., was collected (yield, 0·18 g.) (Found: C, 72·2; H, 7·9. $C_{14}H_{18}O_2$ requires C, 71·8; H, 7·7%). The *semicarbazone* crystallised from alcohol in needles, m. p. 183—184° (Found: C, 61·8; H, 7·3; N, 13·9. $C_{15}H_{21}O_2N_3$ requires C, 61·9; H, 7·2; N, 13·4%).

6-*Keto*-3 : 4-*dimethoxy*-5-*ethyl*-5-γ-*ketobutyl*-5 : 6 : 7 : 8-*tetrahydronaphthalene* (XIV).—The ketone (XIII) (0·9 g.) was dissolved in dry ether (15 c.c.), finely powdered sodamide (0·3 g.) added, and nitrogen passed in slowly at room temperature for 6 hours, the volume being maintained by addition of dry ether from time to time. The methiodide of 4-diethylaminobutan-2-one (from 2·0 g. of the base) was dissolved in alcohol (20 c.c.) and added to the above mixture cooled in ice. After 1½ hours the contents were refluxed for 2 hours. They were then cooled, poured into ice and hydrochloric acid and extracted with ether, and the product isolated in the usual way. A colourless, viscous oil was collected at 148—150° (bath temp.)/0·02 mm. (Found: C, 71·0, 71·0; H, 7·8, 8·2. $C_{18}H_{24}O_4$ requires C, 71·1; H, 7·9%).

7-*Keto*-3 : 4-*dimethoxy*-13-*ethyl*-5 : 6 : 7 : 9 : 10 : 13-*hexahydrophenanthrene* (XV).—The ketone (XIII) (1·0 g.) was dissolved in ether (30 c.c.), finely powdered sodamide (3·5 g.) added, and nitrogen passed in continuously during the reaction. After 5 hours the methiodide of 4-diethylaminobutan-2-one (from 3·0 g. of the base) in alcohol (20 c.c.) was added, and the mixture left overnight in an atmosphere of nitrogen. It was then refluxed for 1½ hours, cooled, poured into ice and hydrochloric acid, and the product isolated with ether. It distilled at 140—150° (bath temp.)/0·02 mm. and crystallised from ether–light petroleum (b. p. 40—60°) in colourless cubes, m. p. 112° (Found: C, 75·0; H, 7·6. $C_{18}H_{22}O_3$ requires C, 75·5; H, 7·7%). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in scarlet-red plates, m. p. 179—180° (Found: N, 11·8. $C_{24}H_{26}O_6N_4$ requires N, 12·0%). 7-Keto-3 : 4-dimethoxy-13-ethyl-5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-octahydrophenanthrene was obtained by reduction of this ketone (0·18 g.) in alcohol (10·0 c.c.) in the presence of platinic oxide. After 1 mol. of hydrogen had been absorbed, the solution was filtered, concentrated, and treated with semicarbazide hydrochloride and sodium acetate in the usual way. The precipitate was collected, washed with water and crystallised from alcohol; m. p. 198—199° alone or mixed with an authentic sample.

The authors are grateful to the Rockefeller Foundation and to the High Commissioner for India for grants. They also wish to acknowledge the valuable help given by Dr. R. Siddiqui in the earlier stages of the investigation.

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141. *Lactones of Glucosaccharic Acid. Part I.* 2 : 5-*Dimethyl* Δ^4-*Glucosaccharo*-3 : 6-*lactone* 1-*Methyl Ester, an Analogue of Ascorbic Acid.*

By F. SMITH.

Methylation of glucosaccharo-1 : 5-3 : 6-dilactone (IV) either with Purdie's reagents or with diazomethane effects isomerisation and gives crystalline 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester (VII). This has also been obtained from glucosaccharo-3 : 6-lactone (III), silver saccharate (V), and glucurone (VI) (Smith, *J. Soc. Chem. Ind.*, 1938, **57**, 450).

The structure of (VII) has been proved by the observation that upon ozonisation it yields oxalic acid and the monomethyl threuronic acid (VIII), the latter being characterised by conversion successively into hydroxymethoxythreosuccinic acid (IX) and the corresponding diamide (X).

Hydrogenation of 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester (VII) and the corresponding acid (XIII) has been carried out, giving 2 : 5-dimethyl 4-deoxyglucosaccharo-3 : 6-lactone 1-methyl ester (XIX) and 2 : 5-dimethyl 4-deoxyglucosaccharo-3 : 6-lactone (XIV) respectively. The diamide (XX) of 2 : 5-dimethyl 4-deoxyglucosaccharic acid was found to give a negative Weerman test for α-hydroxy-amides, thus proving the presence of a 3 : 6-lactone ring in (VII).

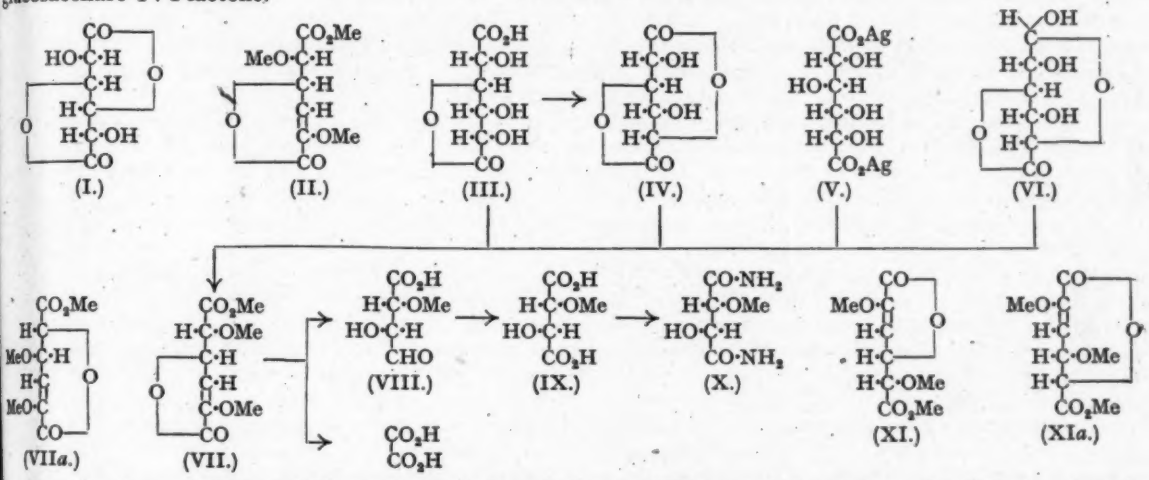
It is suggested that the unsaturated methyl ester (VII) is related to the crystalline substance, obtainable from glucosaccharo-1 : 5-3 : 6-dilactone by the agency of alkaline reagents, which is responsible for the remarkable reducing properties displayed by the dilactone of saccharic acid in alkaline solution or in acid solution after pre-treatment with alkaline reagents.

METHYLATION of mannosaccharo-1 : 4-3 : 6-dilactone (I) either with silver oxide and methyl iodide or with diazomethane causes molecular isomerisation and there is produced an analogue of ascorbic acid, namely, 2 : 5-dimethyl Δ^4-mannosaccharo-3 : 6-lactone 1-methyl ester (II), the structure of which has been elucidated (Haworth, Heslop, Salt, and Smith, this vol., p. 217).

Extension of the investigations to glucosaccharodilactone (IV), first prepared by Rehorst and Scholz (*Ber.*, 1936, **69**, 524) from an impure form of glucosaccharo-3 : 6-lactone (III) (Sohst and Tollens, *Annalen*, 1888, **245**, 1, 19), has shown that (IV) behaves similarly to mannosaccharodilactone (I), resembling it in that both acid groups are internally esterified and in the important respect that it displays reducing properties in alkaline solution, or in acid solution after previous treatment with alkaline reagents. It was expected that these two dilactones would resemble one another in their general reactions, and it seemed highly probable that the novel explanation of the unusual reducing action exhibited by (I) would also serve to explain the reducing properties of (IV). Furthermore, it seemed that the isomerisation of the dilactones (I) and (IV) with alkali, resulting in the development of reducing activity, was bound up with the isomerisation of the dilactones brought about by reagents used in methylation. It was important therefore to examine the nature of the product obtained by methylation of (IV).

Glucosaccharodilactone (IV) behaves similarly to (I) when treated either with Purdie's reagents or with

diazomethane, since it affords a crystalline *compound* to which the structure (VII) has been ascribed. This substance, which may be regarded as arising by simultaneous isomerisation and methylation of the dilactone (IV), can also be obtained by the action of silver oxide and methyl iodide upon glucosaccharo-3 : 6-lactone (III), silver saccharate (V), and glucurone (VI). It is also produced from (III) and saccharic acid by the agency of diazomethane (cf. Schmidt, Dippold, and Zeiser, *Ber.*, 1937, **70**, 2402), and, as will be shown in later communications, (VII) is also derivable from glucosaccharo-1 : 4-lactone, from its 6-methyl ester, from glucosaccharo-3 : 6-lactone 1-methyl ester, and from a new dilactone of saccharic acid prepared from glucosaccharo-1 : 4-lactone.



The structure of the crystalline unsaturated methyl ester (VII) was deduced from the following experimental facts. The substance had a formula $C_9H_{12}O_6$ and it contained three methoxyl groups. Its unsaturated

FIG. 1.

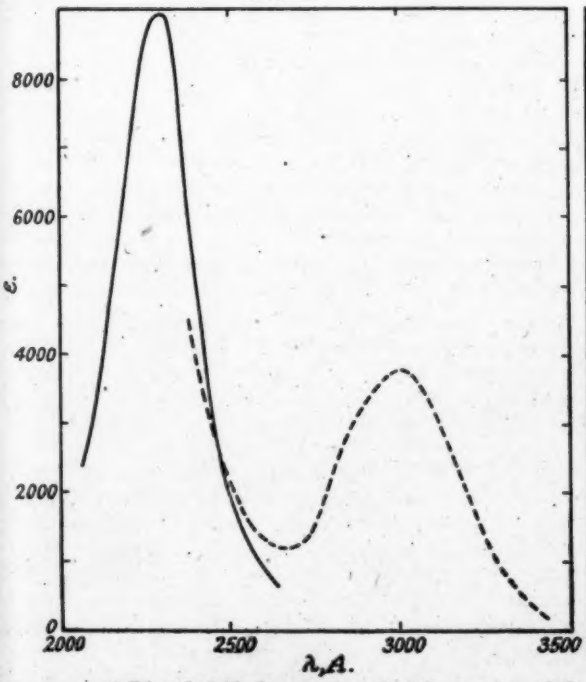
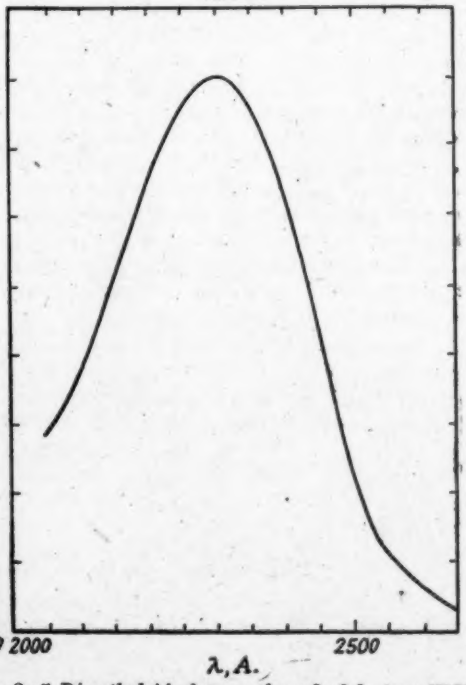


FIG. 2.



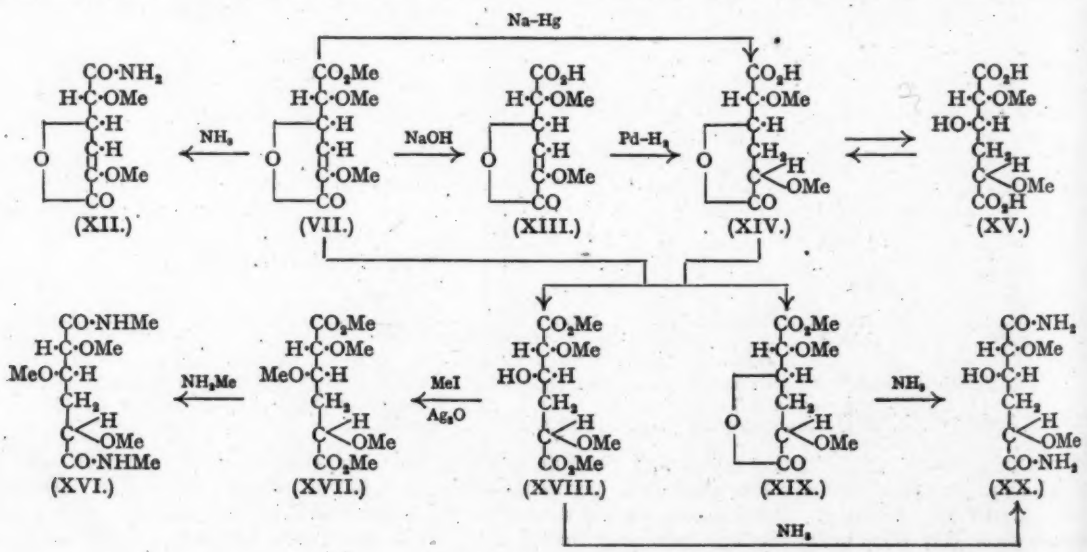
——— 2 : 5-*Dimethyl* Δ^4-*glucosaccharo*-3 : 6-*lactone* 1-*methyl ester* (VII) *in water* (3·3 *mg.*/100 *c.c.*).
------ (VII) *in dilute sodium hydroxide* (10 *mg.*/100 *c.c.*).

2 : 5-*Dimethyl* Δ^4-*glucosaccharo*-3 : 6-*lactone* (XIII) *in water* (3·3 *mg.*/100 *c.c.*).

character was shown by a selective absorption band at λ 2290 A. (see Fig. 1) and by its immediate reaction with chlorine, bromine, and alkaline potassium permanganate. In alkaline solution it reacted with three atomic proportions of iodine. It thus very closely resembled 2 : 5-dimethyl Δ^4-mannosaccharo-3 : 6-lactone 1-methyl ester (II) (Haworth, Heslop, Salt, and Smith, *loc. cit.*). An aqueous solution of the substance

reacted neutral to litmus, but upon warming it combined with 2 equivs. of sodium hydroxide, and in the process 1 mol. of methyl alcohol was eliminated. Hence, the molecule must contain two potentially acidic groups one of which is probably a carbomethoxy-group, and in consequence the other two methyl residues must be etheric in character. Since the substance (VII) reacted with approximately two atomic proportions of chlorine, the presence of one double bond was indicated; this was proved later (see below) by the fact that hydrogenation of (VII) saturates the double bond, producing a dihydro-derivative. Ozonisation of (VII) proceeded smoothly in glacial acetic acid, giving an ozonide which upon decomposition with water afforded oxalic acid and the aldehydic acid (VIII). The latter reduced Fehling's solution actively upon gentle warming but did not restore the colour to Schiff's reagent. The formation of oxalic acid (a 2-carbon fragment) and the aldehydic acid (a 4-carbon fragment) proved that the double bond must be located either between C_2 and C_3 or between C_4 and C_5. Furthermore, the formation of a new carboxyl group and an aldehydic group by the decomposition of the ozonide indicates that the two carbon atoms linked by the double bond must have attached to them a hydrogen atom and a methoxyl group; the system ·CH:C(OMe)· which affords the ·CHO and the new CO_2H group must therefore be present in (VII). Moreover, since oxalic acid and not glyoxylic acid is produced by ozonolysis, it is clear that the methoxy-group, attached to one of the carbon atoms engaged by the ethylenic link, must be joined to that carbon atom adjacent to a terminal CO group which is potentially a carboxyl group as in the system ·CH:C(OMe)·CO·. This grouping also explains the formation of the 4-carbon fragment aldehydic acid. It is plain therefore that the methoxy-group in the system ·CH:C(OMe)·CO· must be attached either to C_2 or to C_5. Oxidation of the aldehydic acid (VIII) with bromine gave hydroxymethoxythreosuccinic acid (IX), identified as its diamide (X). The existence of a hydroxyl group in this 4-carbon fragment reveals the presence of a ring system in the original unsaturated methyl ester (VII). The isolation and characterisation of the acid (IX) as a derivative of threose establishes the configuration of the groups attached to two of the carbon atoms and at the same time accounts for the third methyl group, the other two having already been located, one in the carbomethoxy-group and the other either at C_2 or at C_5 in the grouping ·CH:C(OMe)·CO·. Since the hydroxymethoxysuccinic acid proved to be a derivative of threo- and not of erythro-succinic acid, it is evident that the lactone ring of (VII) must engage C_6 and not C_1, because if the lactone ring did engage C_1 and a hydroxyl group either at C_4 or at C_5 as in (XI) and (XI*a*) then ozonisation followed by oxidation would afford a hydroxymethoxy-derivative of erythro- and not threo-succinic acid (see Haworth, Heslop, Salt, and Smith, *loc. cit.*).

These experimental facts can be explained by the two formulæ (VII) and (VII*a*) and no others, but the evidence at this stage did not allow a choice to be made between these two. The Weerman test (*Rec. Trav. chim.*, 1917, **36**, 16), which has repeatedly proved of high diagnostic value when performed correctly (Ault, Haworth, and Hirst, J., 1934, 1722; cf. Micheel, *Z. physiol. Chem.*, 1933, **218**, 280), was applied in this case to decide which of (VII) and (VII*a*) was correct. This test, which detects a free α-hydroxy-group in an amide without fail (Haworth, Peat, and Whetstone, J., 1938, 1975), can be applied to di- as well as to mono-amides (Smith, J., 1939, 1724; Luckett and Smith, J., 1940, 1106). It will be seen that if formula (VII) is correct, then opening of the lactone ring would liberate a hydroxyl group in the β-position, whereas in the case of formula (VII*a*) the hydroxy-group set free upon the formation of a diamide would be in the α-position and so would be detected by the Weerman test. Treatment of the unsaturated methyl ester with ammonia gave, however, a mono- and not a di-amide, and since this *monoamide* has a strong absorption band at λ 2300 A., characteristic of the original unsaturated ester, it was still believed to possess the unsaturated lactone ring system as in (XII). Therefore the Weerman test could not be applied to this monoamide (XII).



The correct solution to the problem, however, arose during the course of the following series of experiments. Treatment of 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone methyl ester (VII) with a warm solution of sodium hydroxide effects saponification and hydrolysis and there is produced mainly the disodium salt of 2 : 5-dimethyl Δ^4-glucosaccharic acid (see Experimental), which upon acidification affords initially the corresponding dibasic acid. The latter undergoes lactonisation in acidified aqueous solution even at room temperature, giving 2 : 5-*dimethyl* Δ^4-*glucosaccharolactone* (XIII), a crystalline substance which reacts strongly acid to Congo-red paper; it is structurally related to the original unsaturated ester and, like the latter, shows a strong selective absorption band at λ 2290 A. (Fig. 2). The lactone (XIII) reacts directly at room temperature with 1 equiv. of sodium hydroxide, giving a monosodium salt which shows a band at λ 2290 A. and therefore still contains the unsaturated lactone ring system. The monosodium salt is thus analogous to the monoamide (XII). Upon warming with excess of sodium hydroxide, the lactone (XIII) reacts with 2 equivs. of alkali, giving a salt which shows no absorption of ultra-violet light. This observation would appear to indicate that the 5-atom lactone ring as well as the unsaturated grouping is necessary for selective absorption of light (cf. Herbert, Hirst, Percival, Reynolds, and Smith, J., 1933, 1270; Haworth, Hirst, and Smith, J., 1934, 1556). Hydrogenation of the acid lactone (XIII) by means of palladium–charcoal gave crystalline 2 : 5-*dimethyl* 4-*deoxyglucosaccharolactone* (XIV); this was also obtained by reduction of the methyl ester (VII) with sodium amalgam, followed by treatment with dilute sulphuric acid. Esterification of the saturated acid lactone (XIV) with methyl-alcoholic hydrogen chloride yielded the corresponding crystalline *methyl* ester (XIX) (m. p. 77°) together with the open-chain *dimethyl* ester (XVIII) (m. p. 89°). These methyl esters, also obtainable from the unsaturated methyl ester (VII) by hydrogenation in the presence of either a palladium–charcoal catalyst or Raney nickel, are stereochemically related, because upon treatment with ammonia both esters give the same *diamide* (XX) (cf. Smith, *J. Soc. Chem. Ind.*, 1938, **57**, 449). Application of the Weerman test to this diamide gave a negative result, thus proving that the hydroxyl group liberated by amide formation was at C_3 and not at C_2. That a hydroxy-group was really present in the diamide (XX) was shown by the fact that methylation of the dimethyl ester (XVIII) with Purdie's reagents affords methyl 2 : 3 : 5-trimethyl 4-deoxyglucosaccharate (XVII), identified by its transformation into a crystalline *bis-methylamide* (XVI). Confirmation of the structure (VII) and not (VII*a*) for the unsaturated ester is therefore provided.

Further evidence in favour of the presence of a γ-lactone ring in 2 : 5-dimethyl Δ^4-glucosaccharolactone (VII) is forthcoming from the fact that the deoxy-lactone (XIV), having $[\alpha]_D$ + 101° in water, can be readily converted by means of alkali followed by acid into the open-chain dibasic acid, 2 : 5-*dimethyl* 4-*deoxyglucosaccharic acid* (XV), having $[\alpha]_D$ − 22° in water. Thus it is seen that the opening of the lactone ring is accompanied by a rotational change in the negative sense. According to Hudson's rule, this indicates that the lactone ring engages a hydroxy-group on the left-hand side of the carbon chain when the latter is written out according to the Fischer convention (as in the formula above). This will apply only if a 3 : 6-lactone ring obtains as in formula (VII); with a structure (VII*a*) which has a 2 : 6-lactone ring, the opening of the corresponding deoxy-compound would be expected to be accompanied by a rotational change towards a more positive value (cf. Schmidt, Dippold, and Zeiser, *loc. cit.*).

Saturation of the double bond of the 2 : 5-dimethyl Δ^4-glucosaccharolactone methyl ester (VII) and the corresponding acid lactone (XIII) introduces further dissymmetry into the molecule, *viz.*, at C_5, but only one compound was characterised and in this the exact stereochemical arrangement of the substituents at C_5 is as yet unknown.

The investigation upon mannosaccharodilactone and the work now described were undertaken primarily in order to determine why the dilactones of manno- and gluco-saccharic acid display striking reducing properties in alkaline solution, or in acid or neutral solution after pre-treatment with alkaline reagents. As a result of the investigations upon mannosaccharodilactone it was tentatively concluded that the compound produced from it by the agency of alkaline reagents, which shows such strong reducing properties, was related structurally to 2 : 5-dimethyl Δ^4-mannosaccharo-3 : 6-lactone 1-methyl ester (II).

In this connection it is significant that when glucosaccharo-1 : 5-3 : 6-dilactone (IV) is treated with alkaline reagents, there is produced a highly reactive substance (m. p. 159°, $[\alpha]_D$ + 39° in water) isomeric with the dilactone. This crystalline unmethylated substance bears a very close relationship to 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester (VII) : its aqueous solutions exhibit a band at λ 2290 A., show a strongly acid reaction to Congo-red paper, and react immediately with chlorine, bromine, and potassium permanganate; they also reduce hot Fehling's solution and react with iodine in alkaline solution. These facts suggested that the compound (m. p. 159°) is structurally related to (VII) and that it may indeed be the unmethylated form of (VII); the chemistry of this isomeric form of the glucosaccharodilactone will constitute the subject of a later communication.

Experimental.

Preparation of 2 : 5-*Dimethyl* Δ^4-*Glucosaccharo*-3 : 6-*lactone* 1-*Methyl Ester* (VII).—(a) *By the action of diazomethane.* (1) Upon glucosaccharo-1 : 5-3 : 6-dilactone. A solution of the dilactone (1 g.), prepared from glucosaccharo-3 : 6-lactone by Rehorst and Scholz's method (*loc. cit.*), in dry methyl alcohol (10 c.c.) was cooled to − 5°, and an excess of an ice-cold ethereal solution of diazomethane added. There was a brisk evolution of nitrogen. After being kept for 12 hours at − 5°, the solvent and the excess of the diazomethane (indicated by the permanent yellow colour) were removed by distillation under diminished pressure. The syrupy product was redissolved in dry methyl alcohol (10 c.c.), and the treatment with ethereal diazomethane repeated. After several hours at − 5° there separated gradually a

crystalline deposit of 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester. After 12 hours the crystals were filtered off and purified by recrystallisation from ethyl alcohol–ether, m. p. 89°. A further small quantity was obtained from the diazomethane mother-liquors (yield 0·5 g.).

(2) Upon glucosaccharo-3 : 6-lactone. Crude glucosaccharo-3 : 6-lactone (Kiliani, *Ber.*, 1925, **58**, 2344) was purified by crystallisation from dry ether, but owing to its low solubility a continuous-extraction method was employed; the material extracted in the initial stages was syrupy and failed to crystallise, consisting apparently of glucosaccharo-1 : 4-lactone to which reference will be made in a later communication. Subsequent material extracted, however, readily crystallised, and this product proved to be almost pure glucosaccharo-3 : 6-lactone, m. p. 143—144°, $[\alpha]_D^{18°}$ +42° (initial value in water; *c*, 1·0) (Kiliani, *loc. cit.*).

After two treatments with diazomethane in the manner described above for glucosaccharo-1 : 5-3 : 6-dilactone, the glucosaccharolactone (0·8 g.) yielded 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester, m. p. 89° (0·8 g.) (after one crystallisation from ethyl alcohol–ether).

(b) *By the action of Purdie's reagents.* (1) Upon glucosaccharo-1 : 5-3 : 6-dilactone. The crystalline dilactone (1 g.) was methylated with silver oxide and methyl iodide during 8 hours, sufficient dry acetone being added initially to dissolve the dilactone. The partially methylated material was isolated by means of methyl alcohol and treated a second time with Purdie's reagents, no acetone being now added since the product was soluble in methyl iodide. The syrup thus produced was dissolved in hot ether; on standing, 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester separated, m. p. 89° (yield 0·3 g.).

(2) Upon glucosaccharo-3 : 6-lactone. Finely ground saccharolactone (5 g.) was boiled with silver oxide (20 g.) and methyl iodide (30 c.c.) in the presence of dry acetone (5 c.c.). After two more treatments under these conditions, followed by two methylations with silver oxide and methyl iodide alone, the syrupy product appeared to be completely methylated (methoxyl estimation carried out after each methylation). Distillation of the product gave a colourless liquid, b. p. (bath temp.) 180°/0·02 mm., $n_D^{17°}$ 1·4660, which crystallised spontaneously. After crystallisation from ethyl alcohol–ether, the 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester had m. p. 89° (yield 3 g.).

(3) Upon silver saccharate. A solution of glucosaccharo-3 : 6-lactone (1·92 g.) in water (30 c.c.) was treated with N-sodium hydroxide (10·5 c.c.) at room temperature for 15 minutes. A solution of silver nitrate (4·25 g.) in water (20 c.c.) was added with shaking. The white flocculent precipitate gradually became crystalline, and after 1 hour it was filtered off, washed with a small amount of ice-cold water, and dried in a vacuum (yield 1·8 g.) (Found: Ag, 50·5. Calc. for $C_6H_8O_8Ag_2$: Ag, 51·0%). The powdered silver saccharate (1·7 g.) was boiled with methyl iodide (10 c.c.) in the presence of dry methyl alcohol (1 c.c.) for 2 hours, the separation of silver iodide then appearing to be complete. More methyl iodide (10 c.c.) was added, and the methylation continued in the presence of silver oxide (10 g.) in the usual manner. The product was isolated by means of methyl alcohol and methylated completely by two treatments with silver oxide and methyl iodide (no solvent other than methyl iodide was required). The syrup obtained was dissolved in hot ether and nucleated with a crystal of 2 : 5-dimethyl Δ^4-glucosaccharo- 3 : 6-lactone 1-methyl ester. After being kept for 12 hours at − 5°, the crystalline deposit was separated by decantation; one crystallisation from ethyl alcohol–ether gave 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester, m. p. 89° (yield 0·2 g.).

(4) Upon glucurone. Finely powdered glucurone (0·2 g.) was subjected to four methylations with Purdie's reagents, the first being conducted in the presence of dry methyl alcohol (0·5 c.c.) to dissolve the glucurone. The crude, syrupy material isolated by means of methyl alcohol was distilled, giving (i) a mobile liquid, b. p. (bath temp.) 120°/0·03 mm., $n_D^{19°}$ 1·4900, and (ii) a viscous, pale yellow liquid, b. p. (bath temp.) 180°/0·03 mm., which crystallised spontaneously. Removal of adhering syrup from the crystals by trituration with ether–light petroleum, followed by crystallisation from ethyl alcohol–ether, gave 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester, m.p. 89° (yield 60 mg.). This compound was first obtained by Pryde and Williams (*Biochem. J.*, 1933, **27**, 1205) by methylation of glucurone and was termed by them trimethyl glucuralone.

Properties of 2 : 5-*Dimethyl* Δ^4-*Glucosaccharo*-3 : 6-*lactone* 1-*Methyl Ester* (VII).—This *compound*, prepared by any of the methods described above, is a colourless crystalline substance, m. p. 89°, $[\alpha]_D^{19°}$ +98° in water (*c*, 0·7), $[\alpha]_D^{17°}$ +84° in methyl alcohol (*c*, 0·7). It is soluble in water, methyl alcohol, ethyl alcohol, and acetone, much less soluble in ether, and insoluble in light petroleum (Found: C, 50·1; H, 5·7; OMe, 43·1. $C_9H_{12}O_6$ requires C, 50·0; H, 5·6; OMe, 43·1%). An aqueous solution of this ester reacts neutral to litmus paper and it does not reduce boiling Fehling's solution. The unsaturated character of the substance is shown by the fact that it reacts immediately with alkaline potassium permanganate; it reacts slowly with chlorine in aqueous solution (19·7 mg. reacted by direct titration with 7·1 c.c. of 0·02N-chlorine water during 2 hours. Calc. for the addition of 2 Cl: 9·1 c.c.). In a second experiment an aqueous solution of the ester (VII) was allowed to react at room temperature for 15 mins. with an excess of chlorine water. An excess of potassium iodide was added, and the iodine liberated titrated with 0·01N-sodium thiosulphate (20·18 mg. of ester reacted with 11·42 c.c. of 0·02N-chlorine water. Calc. for the addition of 2 Cl: 9·3 c.c.). Bromine water is decolorised, but iodine in potassium iodide is scarcely affected by the ester.

Aqueous solutions of the ester (VII) display strong selective absorption with the head of the band at 2290 A. (ε *ca.* 8500; *c*, 3·3 mg. per 100 c.c.), and upon addition of sodium hydroxide this band disappears, being replaced by one at 3010 A. (ε, *ca.* 3500; *c*, 10 mg. per 100 c.c.) (see Fig. 1).

2 : 5-Dimethyl Δ^4-glucossaccharo-3 : 6-lactone 1-methyl ester is titrated by sodium hydroxide as a γ-lactone; it reacts with 2 equivs. of sodium hydroxide when kept at room temperature for 5—6 hours with excess of the reagent (13·2 mg. reacted with 6·03 c.c. of 0·02N-NaOH, whence equiv. = 109. $C_9H_{12}O_6$ requires equiv., 108). The reaction with sodium hydroxide proceeds to completion in 30 mins. at 50° (14·8 mg. required 6·75 c.c. of 0·02N-sodium hydroxide; equiv. = 109·5). A freshly prepared solution of the ester (VII) in 0·1N-sodium hydroxide shows $[\alpha]_D$ +6° and no change in rotation takes place on warming or keeping the solution. When this alkaline solution, containing the disodium salt, is acidified with a slight excess of sulphuric acid, mutarotation takes place, and the equilibrium value of $[\alpha]_D^{18°}$ +56° is reached in 2—3 hours.

The presence of one ester methoxy-group in the lactone ester was established as follows. A weighed amount of the substance (20—30 mg.) was warmed with 0·3N-barium hydroxide (3 c.c.) for 1½ hours at 55°. The solution was neutralised with carbon dioxide and evaporated to dryness under slightly diminished pressure. These operations were conducted in a Zeisel apparatus, and the methoxyl content of the residue determined in the usual way (Found: residual OMe, 28·3. Calc.: OMe, 28·7%, after the loss of one ester methoxyl group).

The lactone methyl ester (VII) reacts during 30 mins. at room temperature with *ca.* 3 atomic proportions of iodine in alkaline solution. Some iodoform is produced in this reaction (10·84 mg. treated with 20 c.c. of 0·02N-iodine and 12 c.c. of 0·1N-sodium hydroxide, the solution being acidified with dilute sulphuric acid and the excess of the iodine titrated with 0·02N-sodium thiosulphate). A blank experiment was performed at the same time under the same conditions. Iodine equivalent to 7·53 c.c. of 0·02N-sodium thiosulphate was found to have been used up, *i.e.*, 3·005 g.-atoms per g.-mol. Another experiment showed 2·800 g.-atoms.

Treatment of 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester with methyl-alcoholic ammonia at −5° for 24 hours. gave a crystalline *monoamide* (XII). Evaporation of the excess of the solvent in a vacuum over calcium

chloride, followed by crystallisation from ethyl alcohol, gave needles, m. p. 193°, $[\alpha]_D^{18°}$ +75° in water (*c*, 0·3). In aqueous solution this amide has an intense band at 2300 A. (ε, *ca.* 7500; *c*, 5 mg. per 100 c.c.), disappearing upon addition of sodium hydroxide. Such facts suggest that this is a monoamide in which the unsaturated 3 : 6-lactone ring is still intact (Found: C, 48·0; H, 5·7; OMe, 30·5; N, 6·8. $C_8H_{11}O_5N$ requires C, 47·8; H, 5·5; OMe, 30·8; N, 7·0%).

Ozonisation of 2 : 5-*Dimethyl* Δ^4-*Glucosaccharo*-3 : 6-*lactone* 1-*Methyl Ester*.—A solution of the lactonic ester (1·94 g.) in glacial acetic acid (30 c.c.) was treated with a stream of ozonised oxygen at room temperature for 5 hours, the rotation changing from $[\alpha]_D$ +55° (initial value) to $[\alpha]_D$ +14° (constant value). The solution was then diluted with an equal volume of water and freed from solvent by evaporation under diminished pressure. The colourless syrup thus produced evidently contained some undecomposed ozonide because a portion remained insoluble in water. Simultaneous addition and distillation of water under reduced pressure was therefore continued until the syrupy product became completely soluble in water. The syrup obtained consisted of a mixture of 2-hydroxy-3-methoxy-*l*-threuronic acid (VIII) and oxalic acid. The presence of the former was detected by the fact that the syrup reduced Fehling's solution actively on warming, and oxalic acid was readily detected by the formation of calcium oxalate. No glyoxylic acid could be detected (tested with albumin and sulphuric acid).

Oxidation of 2-*Hydroxy*-3-*methoxy*-l-*threuronic Acid to Hydroxymethoxythreosuccinic Acid* (IX).—The syrupy product obtained from the previous experiment was dissolved in water (30 c.c.) and neutralised by warming with barium carbonate. The precipitate, consisting of barium oxalate and the excess of barium carbonate, was filtered off and washed with water. The amount of oxalic acid in the precipitate was determined by dissolving it in hot sulphuric acid and titrating it with 0·1N-potassium permanganate solution (yield of oxalic acid, 70%). The combined mixture of filtrate and washings, which still reduced Fehling's solution strongly on warming, was treated with bromine (1 c.c.) for 2 days at room temperature. The solution, now non-reducing to Fehling's solution, was freed from the excess of bromine by aeration, and neutralised with silver oxide. The silver bromide was filtered off, and silver ions in solution were precipitated as sulphide by passing hydrogen sulphide. Removal of the silver sulphide by filtration, followed by removal of the solvent under diminished pressure, gave a pale yellow, glassy product which was the acid barium salt of hydroxymethoxythreosuccinic acid. This salt was acid to Congo-red paper and gave a positive test for barium. It did not reduce Fehling's solution even on prolonged boiling.

Dimethyl Hydroxymethoxythreosuccinate.—The foregoing acid barium salt was esterified by boiling for 8 hours with 3% methyl-alcoholic hydrogen chloride (100 c.c.). The solution was cooled, neutralised with silver carbonate, filtered after the addition of a little charcoal, and then freed from solvent by evaporation under slightly diminished pressure. Distillation of the syrupy product gave methyl hydroxymethoxythreosuccinate, a colourless, mobile liquid (0·55 g.), b. p. (bath temp.) 110°/0·01 mm., $n_D^{18°}$ 1·4410, $[\alpha]_D^{19°}$ +48·5° in methyl-alcohol (*c*, 0·8) (Found: equiv., by hydrolysis with hot 0·02N-sodium hydroxide, 99; OMe, 48·5. Calc. for $C_7H_{12}O_6$: equiv., 96; OMe, 48·5%).

Treatment of this threosuccinate with methyl-alcoholic ammonia for 2 days at −5° readily gave the corresponding diamide. Removal of the solvent in a vacuum over anhydrous calcium chloride, followed by recrystallisation from methyl alcohol, gave an almost quantitative yield of hydroxymethoxythreosuccinamide (X), m. p. and mixed m. p. 201° (decomp.), $[\alpha]_D^{20°}$ +115° in water (*c*, 0·5), $[\alpha]_D^{20°}$ +140° in methyl alcohol (*c*, 0·4) (Found: C, 37·1; H, 6·2; OMe, 18·8; N, 17·3. Calc. for $C_5H_{10}O_4N_2$: C, 37·0; H, 6·2; OMe, 19·1; N, 17·3%).

2 : 5-*Dimethyl* Δ^4-*Glucosaccharo*-3 : 6-*lactone* (XIII).—A solution of the 1-methyl ester (VII) (0·5 g.) in 0·1N-sodium hydroxide (52 c.c.) was warmed for 1½ hours at 55°, then treated with 0·1N-sulphuric acid (51·8 c.c.) and evaporated to dryness under diminished pressure at 40°. Several extractions of the solid residue with acetone gave, upon removal of the solvent, crystalline 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone, m. p. 168°, $[\alpha]_D^{16°}$ +73·5° in water (*c*, 0·7) (constant for 3 days). The compound reacted acid to litmus and Congo-red paper; it did not reduce boiling Fehling's solution (Found: C, 47·35; H, 5·0; OMe, 30·8. Calc. for $C_8H_{10}O_6$: C, 47·5; H, 5·0; OMe, 30·7%) (see Schmidt, Dippold, and Zeiser, *loc. cit.*).

The free carboxyl group in this lactonic acid can be titrated directly with sodium hydroxide at room temperature, 1 equiv. being required (14·27 mg. required 3·55 c.c. of 0·02N-sodium hydroxide for neutralisation; whence equiv., 200. $C_8H_{10}O_6$ requires equiv., 202). Upon heating for 1 hour at 50° 2 equivs. of sodium hydroxide are required for neutralisation (14·27 mg. required 7·0 c.c. of 0·02N-sodium hydroxide; whence equiv., 102. $C_8H_{10}O_6$ requires equiv., 101).

The unsaturated character of (XIII) is shown by the fact that it reacted with chlorine (1 mol. reacted by direct titration with 1·5 atoms during 3 hours), decolorised bromine, and also decolorised an alkaline solution of potassium permanganate. It shows an intense absorption band at 2290 A. (ε, *ca.* 8000; *c*, 3·3 mg. per 100 c.c.) (Fig. 2). The addition of 1 equiv. of sodium hydroxide does not affect the absorption appreciably, since the alkali reacts with the carboxyl group while the unsaturated furone ring remains unaffected; this is also supported by the specific rotation of the monosodium salt, $[\alpha]_D$ +64°. After keeping with slight excess of sodium hydroxide, the rotation of the unsaturated acid falls gradually to a constant value of $[\alpha]_D$ +2·5° (*ca.*) and simultaneously the intensity of the band at λ 2290 A. decreases until, at the equilibrium point, when only the disodium salt is present in solution, the solution shows no selective absorption. Acidification liberates the dibasic acid, which undergoes fairly rapid mutarotation, with the formation of the original 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone: $[\alpha]_D$ ±0° (initial value of free dibasic acid in solution); +47·5° (after 17 mins.); +66° (52 mins.); +74° (112 mins.) (constant value). Concurrently with this mutarotation the band at λ 2300 A. appears, and at the equilibrium point the intensity of the band is equal to that of the original value of the 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone.

In alkaline solution this lactone, like the ester, reacts with approximately 3 atomic proportions of iodine (10·53 mg. reacted with 7·05 c.c. of 0·02N-iodine in alkaline solution, *i.e.*, 1 mol. reacts with 2·690 atoms); 3 minutes after the mixing, a small precipitate of iodoform was formed.

Regeneration of the 1-*Methyl Ester* (VII) *from the Lactone* (XIII).—(*a*) *With Purdie's reagents*. One treatment of 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone (145 mg.) with silver oxide (0·5 g.) and methyl iodide (5 c.c.) in the presence of methyl alcohol (0·1 c.c.) during 8 hours regenerated the ester in almost quantitative yield, m. p. and mixed m. p. 89° (after isolation by means of acetone followed by recrystallisation from ethyl alcohol–ether).

(*b*) *With acid methyl alcohol*. The lactone (100 mg.) was boiled for 6 hours with 2% methyl-alcoholic hydrogen chloride (10 c.c.). Neutralisation of the mineral acid with silver carbonate, followed by removal of the solvent under slightly diminished pressure, gave the 1-methyl ester (90 mg.), m. p. and mixed m. p. 89° (after one crystallisation from ethyl alcohol–ether).

Hydrogenation of 2 : 5-*Dimethyl* Δ^4-*Glucosaccharo*-3 : 6-*lactone* (XIII).—A solution of the lactone (1·0 g.) in dry methyl alcohol (30 c.c.) was shaken for 1 day at room temperature in hydrogen at *ca.* 1·5 atm. in the presence of a palladium–charcoal catalyst. The solution, which was then transparent to ultra-violet light, was filtered and evaporated to dryness. In this manner there was obtained a colourless, viscous syrup which reacted acid to Congo-red paper and showed no selective absorption band (tested at 20 mg. per 100 c.c.). The product crystallised spontaneously and, after removal of adhering syrup from the crystals by trituration with ether–light petroleum followed by recrystallisation

from acetone, the 2 : 5-*dimethyl* 4-*deoxyglucosaccharo*-3 : 6-*lactone* (XIV) (*ca.* 0·1 g.) had m. p. 130°, $[\alpha]_D^{18°}$ +72° in methyl alcohol (*c*, 0·9), $[\alpha]_D$ +101° initial value in water (*c*, 2·0); +90·5° (after 15 hours); +53·5° (74 hours); +22·5° (267 hours) (Found: C, 46·9; H, 6·0; OMe, 30·3; by titration at room temp., equiv., 198; by titration hot, equiv., 98. $C_8H_{12}O_6$ requires C, 47·1; H, 5·9; OMe, 30·4%; equiv., monobasic, 204; equiv., dibasic, 102).

The syrup obtained from the mother-liquors after the separation of the lactone (XIV) was esterified by boiling for 8 hours with 1·2% methyl-alcoholic hydrogen chloride (50 c.c.). Neutralisation of the solution with silver carbonate, followed by removal of the solvent under reduced pressure, gave a colourless liquid (0·89 g.), b. p. (bath temp.) 155—160°/0·02 mm., which crystallised immediately. Several crystallisations from ethyl alcohol–ether yielded *methyl* 2 : 5-*dimethyl* 4-*deoxyglucosaccharate* (XVIII) as colourless plates, m. p. 89° [depressed by admixture with the 1-methyl ester (VII)]; $[\alpha]_D^{18°}$ −13° initial value in water (*c*, 1·0); −2° (after 14 hours); ±0° (46 hours); +5° (264 hours). The compound did not titrate as a lactone, but upon heating to 50°, 8·72 mg. reacted with 3·75 c.c. 0·02N-sodium hydroxide corresponding to equiv., 116 (Calc.: 125) [Found: C, 48·15; H, 7·35; OMe, 49·2; OMe, 23·8 (after hydrolysis with barium hydroxide). $C_{10}H_{18}O_7$ requires C, 48·0; H, 7·3; OMe, 49·6; residual OMe after saponification, 24·8%].

Fractional crystallisation of the crystalline residue obtained from the mother-liquors, after the compound (XVIII) had been separated, gave further crops of crystals which formed needles, m. p. 77°, from ether–alcohol. This compound, more soluble than (XVIII) in ether–alcohol, separated well from ethyl alcohol–ether–light petroleum, and had m. p. 77°. It proved to be 2 : 5-*dimethyl* 4-*deoxyglucosaccharo*-3 : 6-*lactone* 1-*methyl ester* (XIX) and had $[\alpha]_D^{17°}$ +117° in water (*c*, 0·9) (no mutarotation) (Found: C, 49·3; H, 6·4; OMe, 42·6. $C_9H_{14}O_6$ requires C, 49·5; H, 6·5; OMe, 42·6%).

Hydrogenation of 2 : 5-*Dimethyl* Δ^4-*Glucosaccharo*-3 : 6-*lactone* 1-*Methyl Ester* (VII).—(*a*) A solution of the ester (1·2 g.) in dry methyl alcohol (50 c.c.) was shaken at room temperature in hydrogen at approx. 1·5 atm. in the presence of a palladium–charcoal catalyst. The rapid absorption of hydrogen appeared to be complete within 10 minutes, for after a further 2 hours' shaking very little more had been absorbed and the solution showed no selective absorption (tested at 24 mg. per 100 c.c.). The catalyst was filtered off, washed with methyl alcohol, and the solution evaporated to a crystalline residue. Crystallisation from acetone–ether gave mainly methyl 2 : 5-dimethyl 4-deoxyglucosaccharate (XVIII), m. p. 89° alone or in admixture with that obtained by hydrogenation of the lactone (XIII); $[\alpha]_D^{21°}$ −13·5° in water (*c*, 1·2) (Found: OMe, 49·6%).

From the mother-liquors a crystalline residue, consisting of a mixture of (XVIII) (m. p. 89°) and (XIX) (m. p. 77°) was obtained. Two crystallisations from water completely separated these two compounds, the former being much more soluble than the latter. One further crystallisation of the needles which had separated from aqueous solution yielded the ester of m. p. 77°, $[\alpha]_D^{18°}$ +117° in water (*c*, 0·8) (Found: OMe, 42·6%).

(*b*) A solution of the lactone ester (VII) (0·5 g.) in water (50 c.c.) was vigorously shaken in hydrogen at approx. 1·5 atm. in the presence of a Raney nickel catalyst. The uptake of hydrogen was very rapid, and after 45 minutes the solution was filtered, evaporated to dryness under diminished pressure, and the residue purified by extraction with acetone. The crystalline product, m. p. 67°, $[\alpha]_D^{18°}$ +180° in water (*c*, 2·8), was a mixture of the same two esters as were formed in (*a*), above. The product was therefore hydrolysed by heating for 30 mins. at 60° with 2 equivs. of 0·1N-sodium hydroxide. Addition of 2 equivs. of 0·1N-sulphuric acid, followed by evaporation of the solution to dryness under reduced pressure and extraction of the residue with acetone, gave a crystalline substance, m. p. 142°, composed of a mixture of 2 : 5-dimethyl 4-deoxyglucosaccharo-3 : 6-lactone (XIV) and 2 : 5-dimethyl 4-deoxyglucosaccharic acid (XV). It was heated to 5° above its m. p. in an oil-bath for 10 mins. and then allowed to cool. Recrystallisation from water yielded 2 : 5-dimethyl 4-deoxyglucosaccharo-3 : 6-lactone (XIV), m. p. and mixed m. p. (see below) 129°, $[\alpha]_D^{21°}$ +97° in water (*c*, 1·5) (Found: C, 47·2; H, 5·8; OMe, 30·5. Calc. for $C_8H_{12}O_6$: C, 47·1; H, 5·9; OMe, 30·4%).

Reduction of 2 : 5-*Dimethyl* Δ^4-*Glucosaccharo*-3 : 6-*lactone* 1-*Methyl Ester* (VII) *with Sodium Amalgam.*—A solution of the ester (0·7 g.) in water (60 c.c.) was vigorously stirred and treated with small portions of 2·5% sodium amalgam. From time to time the excess of sodium hydroxide was neutralised by careful addition of 4N-hydrochloric acid. After the addition of 140 g. of amalgam (during *ca.* 8 hours), the solution had no selective absorption in the ultra-violet. After separation of the mercury, the solution was acidified with N-sulphuric acid, concentrated under diminished pressure to eliminate carbon dioxide, and neutralised with N-sodium hydroxide. The free organic acid was liberated from its disodium salt by addition of 0·088N-hydrochloric acid (70·0 c.c. Calc.: 73·7 c.c.). The solution was evaporated to dryness under reduced pressure, and the organic acid extracted with acetone. Removal of the solvent under diminished pressure gave a pale yellow syrup (0·65 g.) which crystallised immediately. Recrystallisation from ethyl acetate gave 2 : 5-dimethyl 4-deoxyglucosaccharo-3 : 6-lactone (XIV), m. p. 130° alone or in admixture with that previously obtained, $[\alpha]_D^{20°}$ +102° in water (*c*, 1·0) (Found: OMe, 30·3%).

Esterification of 2 : 5-*Dimethyl* 4-*Deoxyglucosaccharo*- 3 : 6-*lactone.*—The pure crystalline acid lactone (m. p. 130°, 0·3 g.) was boiled for 8 hours with 2% methyl-alcoholic hydrogen chloride (40 c.c.). Neutralisation of the solution with silver carbonate, followed by removal of the solvent, gave methyl 2 : 5-dimethyl 4-deoxyglucosaccharate (XVIII), m. p. and mixed m. p. 89°.

Treatment of Methyl 2 : 5-*Dimethyl* 4-*Deoxyglucosaccharate* (XVIII) *with Ammonia.*—The ester (XVIII) (210 mg.) was treated with methyl-alcoholic ammonia for 15 hours at −5°. The crystals which had separated from the solution were filtered off and washed with ethyl alcohol and ether. After recrystallisation from water the *diamide* (XX) of 2 : 5-*dimethyl* 4-*deoxyglucosaccharic acid* had m. p. 270° (decomp.) (Found: C, 43·7; H, 7·4; OMe, 28·3; N, 12·8. $C_8H_{16}O_5N_2$ requires C, 43·6; H, 7·35; OMe, 28·2; N, 12·7%). When tested under carefully controlled conditions (see p. 512), this diamide gave a negative Weerman test for α-hydroxy-amides. In a control experiment, carried out simultaneously, the diamide of 2 : 3 : 4-trimethyl mucic acid gave, upon treatment with 1·5N-sodium hypochlorite, sodium *iso*cyanate, detected by its transformation into hydrazodicarbonamide upon the addition of semicarbazide.

Evaporation of the solvent from the methyl-alcoholic ammonia solution from which the diamide (XX) had been separated gave a *monoamide*, m. p. 144° (after one crystallisation from ethyl alcohol and one from ethyl alcohol–ether), $[\alpha]_D^{18°}$ −20° in water (*c*, 1·4) (Found: C, 46·1; H, 7·3; OMe, 40·3; N, 5·9. $C_9H_{17}O_6N$ requires C, 45·9; H, 7·3; OMe, 39·6; N, 6·0%).

Treatment of 2 : 5-*Dimethyl* 4-*Deoxyglucosaccharo*-3 : 6-*lactone* 1-*Methyl Ester* (XIX) *with Ammonia.*—The ester (50 mg.; m. p. 77°) was treated for 2 days at −5° with methyl-alcoholic ammonia. The crystals formed were separated by decantation and recrystallised from water, affording the above diamide (XX), m. p. 268° (decomp.) alone or in admixture with that recorded above.

Treatment of Methyl 2 : 5-*Dimethyl* 4-*Deoxyglucosaccharate with Methylamine.*—With methylamine in methyl alcohol the ester (m. p. 89°) gave a *bismethylamide* which readily separated from the methyl-alcoholic methylamine solution; m. p. 221° after crystallisation from ethyl alcohol, $[\alpha]_D^{18°}$ −13·5° in water (*c*, 2·5) (Found: C, 48·6; H, 8·4; OMe, 24·8; N, 11·7. $C_{10}H_{20}O_5N_2$ requires C, 48·4; H, 8·15; OMe, 25·0; N, 11·3%).

Methyl 2 : 3 : 5-*Trimethyl* 4-*Deoxyglucosaccharate* (XVII).—Four treatments of methyl 2 : 5-dimethyl 4-deoxyglucosaccharate (100 mg.) with silver oxide and methyl iodide gave *methyl* 2 : 3 : 5-*trimethyl* 4-*deoxyglucosaccharate* (isolated

after each methylation by means of acetone) as a colourless liquid, b. p. 130°/0·05 mm., $n_D^{23°}$ 1·4406, $[\alpha]_D^{23°}$ −8° in water (*c*, 2·3) (Found: OMe, 56·1; and after hydrolysis with alkali, OMe, 27·0. $C_{11}H_{20}O_7$ requires OMe, 58·7, 35·2%, respectively). Treatment of this methyl ester (XVII) with methylamine in methyl alcohol yielded the *bismethylamide* (XVI) of 2 : 3 : 5-trimethyl 4-deoxyglucosaccharic acid, m. p. 168° (after crystallisation from acetone), $[\alpha]_D^{20°}$ −10·5° in water (*c*, 3·3) (Found: C, 50·3; H, 8·5; N, 10·4; OMe, 35·5. $C_{11}H_{22}O_5N_2$ requires C, 50·4; H, 8·5; N, 10·7%; OMe, 35·5).

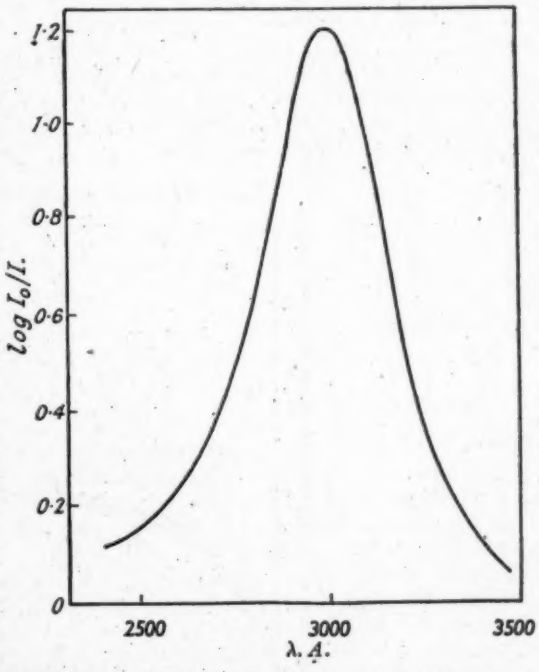
2 : 5-*Dimethyl* 4-*Deoxyglucosaccharic Acid* (XV).—A solution of crystalline methyl 2 : 5-dimethyl 4-deoxyglucosaccharate (0·35 g.) in water (5 c.c.) was heated with N-sodium hydroxide (5 c.c.) for one hour at 55°. The solution was then treated with 0·1N-sulphuric acid (49 c.c.) and evaporated to dryness under reduced pressure. Extraction of the dry crystalline residue with acetone, followed by filtration and removal of the solvent, gave the *acid* (XV), m. p. 161°, $[\alpha]_D^{18°}$ −22° initial value in water (*c*, 1·3), changing in 14 weeks to ±0° (after recrystallisation from acetone or acetone–ether). This reacted acid to Congo-red paper and could be titrated directly with sodium hydroxide solution (Found: C, 43·1; H, 6·3; OMe, 28·2; equiv., 108. $C_8H_{14}O_7$ requires C, 43·25; H, 6·4; OMe, 28·2%; equiv., 111).

The acid (XV) readily lost 1 mol. of water when heated in a capillary tube above its m. p., effervescing and then crystallising upon cooling to form the lactone (XIV), m. p. 130°. The same transformation is readily accomplished by sublimation in a vacuum (0·01 mm.) at 165°, the sublimate being pure 2 : 5-dimethyl 4-deoxyglucosaccharo-3 : 6-lactone, m. p. 131° alone or in admixture with a specimen obtained as on p. 516; $[\alpha]_D^{18°}$ +105° (initial value in water; *c*, 0·7) (Found: OMe, 30·5%).

The Effect of Sodium Hydroxide upon 2 : 5-*Dimethyl* Δ^4-*Glucosaccharo*-3 : 6-*lactone* 1-*Methyl Ester* (VII).—As reported on p. 513, this ester is saponified at 55° to give the free lactone (XIII). Both the ester and the lactone are unsaturated and exhibit intense selective absorption at λ 2300 A. (Figs. 1 and 2). In alkaline solution the lactonic acid is transparent to ultraviolet light, whereas (see p. 514) its ester has a strong band at λ 3010 A. (ε, *ca.* 3500) in alkaline solution (Fig. 1) and a band at λ 2900 A. remains after the alkaline solution has been heated. This curious observation has not yet been studied fully, but the experimental facts would appear to indicate that when 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester is treated with alkaline reagents there is formed, in addition to the main product (the sodium salt of 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone), a new compound characterised by a selective absorption band at λ 3010 A. in alkaline solution. Some support for this theory was obtained as follows.

A solution of the lactone ester (VII) (102 mg.) in 0·1N-sodium hydroxide (11·3 c.c.) (solution showed a band at λ 3010 A.) was warmed for 1 hour at 60°, then treated with 0·1N-sulphuric acid (11·2 c.c.) and evaporated to dryness under diminished pressure. Extraction of the dry residue with acetone–ethyl alcohol gave a crude crystalline acid product, showing a band at λ 2900 A. in dilute sodium hydroxide solution (ε, *ca.* 3500; *c*, 10 mg. per 100 c.c.), from which pure 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone could be separated, m. p. and mixed m. p. 168° (no band in sodium hydroxide solution).

FIG. 3.



From a number of preparations of this lactone the yellowish, partly crystalline residues from the mother-liquors were combined. Distillation of these in a vacuum (200—230°/0·03 mm.) gave a pale yellow crystalline sublimate. Three crystallisations from water yielded pale yellow crystals, m. p. 266° (decomp.) (Found: OMe, 30·7. $C_8H_{10}O_6$ requires OMe, 30·65%), which reacted acid to litmus paper. This crystalline compound exhibits a strong selective absorption band at λ 3010 A. (ε, *ca.* 24,000; *c*, 1 mg. per 100 c.c. in 50% aqueous ethyl alcohol), moving on addition of sodium hydroxide to λ 2920 A. (ε, *ca.* 24,000; *c*, as before) (see Fig. 3). The analytical and absorption data suggest that this *compound* is formed from 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone by introduction of a double bond into the molecule between C_2 and C_3, thus giving a conjugated system of four double bonds.

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[*Received, June 1st*, 1944.]

142. *The Constitution of Trimethylene Sorbitol.*

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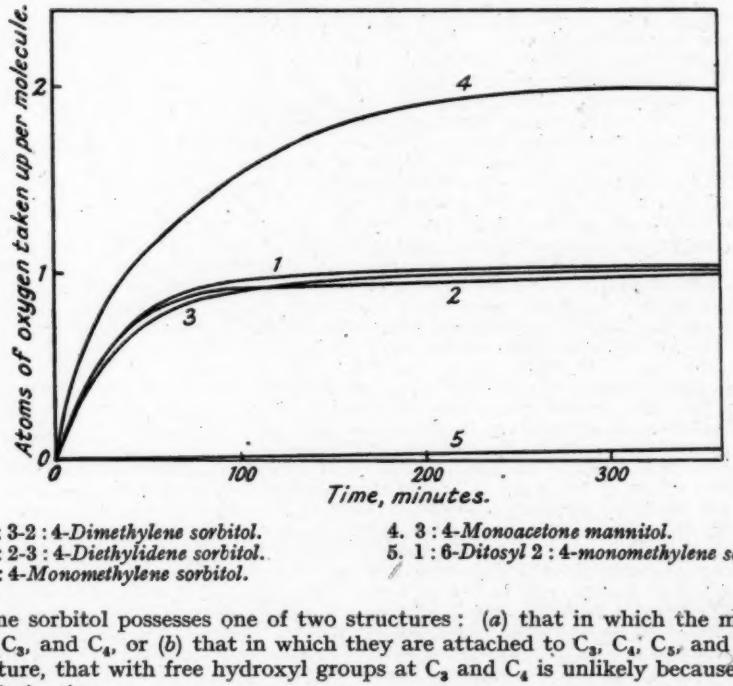
Trimethylene sorbitol is progressively hydrolysed by dilute acid to give a di- and a mono-methylene sorbitol. Evidence is presented which shows that these compounds are 1 : 3-2 : 4-5 : 6-trimethylene sorbitol, 1 : 3-2 : 4-dimethylene sorbitol, and 2 : 4-monomethylene sorbitol, respectively.

ALTHOUGH trimethylene sorbitol was first described by Schultz and Tollens in 1896 (*Annalen*, **289**, 23), yet the precise orientation of the formaldehyde residues has apparently not been determined. This we have now been able to do as a result of a study of the products of the graded hydrolysis of the trimethylene compound. In the course of this and other work concerned with the methylene derivatives of hexitols and saccharic acids (see, *e.g.*, Haworth and Wiggins, this vol., pp. 58, 155), we have observed that cyclic acetal formation with formaldehyde gives much more stable structures than with other aldehydes such as benzaldehyde or

acetaldehyde. For instance, 70% acetic acid at 100° failed to effect hydrolysis of the methylene groups, whereas the same reagent rapidly removes one acetaldehyde residue from triethylidene sorbitol (Appel, J., 1935, 425). Trimethylene sorbitol is hydrolysed, however, by 0·1N-sulphuric acid in 40 hours and by N-sulphuric acid in 2 hours, the time being that required for the attainment of a constant rotation. From the hydrolysate a *dimethylene sorbitol* (soluble in chloroform) and a *monomethylene sorbitol* (insoluble in chloroform but soluble in methyl alcohol) were separated, by virtue of these solubility differences, in yields of 31% and 14% respectively. Treatment of either of these with paraformaldehyde and concentrated sulphuric acid gave trimethylene sorbitol (m. p. 213°), identical with the original material.

The dimethylene sorbitol formed a crystalline *monotrityl* derivative, a fact strongly indicating the presence of one primary hydroxyl group. It also formed a *monobenzoate*, a *dibenzoate*, a *dimethyl* derivative, and a *diacetate*, all crystalline. Evidence of the presence of two free hydroxyl groups at adjacent carbon atoms was obtained by oxidation with lead tetra-acetate solution according to the procedure of Hockett and McClenahan (*J. Amer. Chem. Soc.*, 1939, **61**, 1667), whereby it was found that the initial rapid reaction ceased after one atomic proportion of oxygen per molecule of dimethylene sorbitol had been consumed. A comparative experiment was carried out with diethylidene sorbitol in which it was known that hydroxyl groups were present on C_5 and C_6 (Appel, *loc. cit.*). The graph of the rate of oxidation follows almost exactly that for dimethylene sorbitol (see figure).

Rates of oxidation of hexitol derivatives with lead tetra-acetate.



1. 1 : 3-2 : 4-*Dimethylene sorbitol.*
2. 1 : 2-3 : 4-*Diethylidene sorbitol.*
3. 2 : 4-*Monomethylene sorbitol.*
4. 3 : 4-*Monoacetone mannitol.*
5. 1 : 6-*Ditosyl* 2 : 4-*monomethylene sorbitol.*

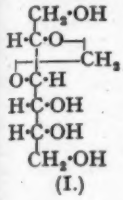
Thus dimethylene sorbitol possesses one of two structures: (*a*) that in which the methylene groups are attached to C_1, C_2, C_3, and C_4, or (*b*) that in which they are attached to C_3, C_4, C_5, and C_6 of sorbitol. The third possible structure, that with free hydroxyl groups at C_3 and C_4 is unlikely because of the formation of a triphenylmethyl derivative.

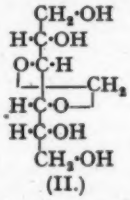
Diethylidene sorbitol, which is known to have free hydroxyl groups on C_5 and C_6 (Appel, *loc. cit.*), was methylated, and 5 : 6-*dimethyl diethylidene sorbitol* obtained. When this was treated with paraformaldehyde and concentrated sulphuric acid simultaneous hydrolysis of the acetaldehyde groups and methylenation occurred, and there was obtained a crystalline 5 : 6-dimethyl dimethylene sorbitol. The dimethylene sorbitol under discussion was now methylated, and the dimethyl derivative so obtained had the same m. p. and specific rotation as the 5 : 6-dimethyl dimethylene sorbitol prepared as just described. Moreover, a mixture of the two substances showed no depression of m. p. It is clear, therefore, that in dimethylene sorbitol the hydroxyl groups on C_1, C_2, C_3, and C_4 are involved in acetal formation with two residues of formaldehyde.

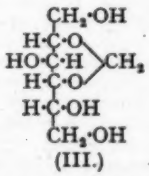
The actual orientation of the methylene linkages in dimethylene sorbitol was ascertained from a study of the monomethylene sorbitol produced at the same time by the hydrolysis of trimethylene sorbitol. In view of the fact that both the mono- and the di-methylene sorbitol yield the original trimethylene compound when methylenated, it is reasonable to assume that the hydrolysis of the trimethylene compound is progressive and that monomethylene sorbitol arises through dimethylene sorbitol.

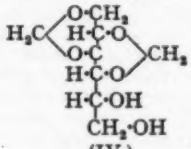
Monomethylene sorbitol contains two primary alcohol groups inasmuch as it yields a *ditrityl* and a *ditosyl* derivative, the latter compound being converted by sodium iodide in acetone into a crystalline *di-iodo monomethylene sorbitol*. We have seen that in the dimethylene sorbitol, C_5 and C_6 are not involved in acetal formation, and this must also be true of the monomethylene compound. It follows from these observations that

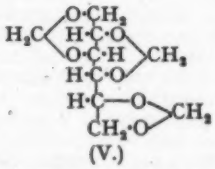
the formaldehyde residue in monomethylene sorbitol must be attached to one of the following pairs of atoms: C_1 and C_2 (I); C_3 and C_4 (II); C_2 and C_4 (III).


(I.)


(II.)


(III.)


(IV.)


(V.)

A decision has been reached between these possibilities by studying the rates of oxidation of monomethylene sorbitol and of its ditosyl derivative with lead tetra-acetate: 1 mol. of monomethylene sorbitol used up one atom of oxygen, indicating the presence of one glycol group only (*i.e.*, a group with free hydroxyls on adjacent carbon atoms). Inspection of (II) shows the presence of two glycol groups, and therefore two atoms of oxygen would be consumed, as was indeed the case in a comparative experiment with 3 : 4-monoacetone mannitol (see figure). Treatment of the 1 : 6-ditosyl derivative of monomethylene sorbitol with lead tetra-acetate showed that no glycol group was present in this compound, an observation which eliminates (I) as a possible structure. Thus the methylene group in monomethylene sorbitol must be attached to C_2 and C_4 and the substance is represented by (III).

Since 2 : 4-monomethylene sorbitol arises from 1 : 2-3 : 4-dimethylene sorbitol it follows that the latter substance is 1 : 3-2 : 4-dimethylene sorbitol (IV) and that the original trimethylene compound is 1 : 3-2 : 4-5 : 6-trimethylene sorbitol (V).

Pentonic acid derivative.	M. p.	$[\alpha]_D$ in chloroform.	M. p. of amide.
Dimethylene pentonic acid methyl ester from dimethylene sorbitol ...	200°	−33·0°	267°
Methyl dimethylene d-*arabonate* (high melting)	200—201	−31·1	268
Methyl dimethylene l-*arabonate*	200—201	+34·1	268
Methyl dimethylene d-*xylonate*	200	+32·0	267

An alternative method of establishing the constitution of dimethylene sorbitol consisted in its oxidation first with lead tetra-acetate and then with bromine water, and an examination of the carboxylic acid so produced. Analysis of the product obtained corresponded with its being a dimethylene pentonic acid, and clearly this pentonic acid would have the configuration either of *l*-xylose or of *d*-arabinose according as the glycol group in the dimethylene sorbitol was at the 5 : 6- or at the 1 : 2-position. The method was not diagnostic, however, and had to be abandoned because the physical properties (*i.e.*, m. p. and specific rotation) of the derivatives of xylonic acid and arabonic acids under consideration were not sufficiently different. This similarity of properties is shown in the above table. For the purpose of this comparison the dimethylene derivatives of *d*- and *l*-arabonic acid and *d*-xylonic acid were synthesised from *d*-arabinose, *l*-arabinose, and *d*-xylose, respectively.

Experimental.

Preparation of Trimethylene Sorbitol.—(*a*) *By using hydrochloric acid and* 38% *formalin solution.* (i) Sorbitol (20 g.), 38% formalin solution (20 c.c.), and fuming hydrochloric acid (20 c.c.) were heated together under reflux for 1½ hours. The solution was cooled, and extracted with 20-c.c. portions of chloroform until all the chloroform-soluble material was removed. The combined chloroform extracts were washed successively with water, 0·5N-sodium hydroxide, and again with water, dried over anhydrous magnesium sulphate, and evaporated to dryness. Crystallisation of the residue three times from ethyl alcohol gave a mass of colourless needles (1·1 g.; 4·6%), m. p. 206°. Schultz and Tollens (*loc. cit.*) record m. p. 206° for trimethylene sorbitol.

(ii) 38% Formalin solution (20 c.c.) containing sorbitol (20 g.) was saturated with hydrogen chloride, and the solution shaken overnight with chloroform (20 c.c.). The mixture was extracted with successive quantities of chloroform, the extracts combined, washed with water, 0·5N-sodium hydroxide, and again with water, dried over anhydrous magnesium sulphate, and evaporated to dryness. After recrystallisation from ethyl alcohol the trimethylene sorbitol (2·5 g.; 10·5%) had m. p. 206°.

(*b*) *By using concentrated sulphuric acid and paraformaldehyde.* Sorbitol (10 g.), paraformaldehyde (10 g.), and concentrated sulphuric acid (10 c.c.) were stirred together. The mixture became quite warm and, after it had cooled to room temperature again, chloroform (100 c.c.) was added and the mixture shaken for 4 hours. The chloroform was decanted and the extraction process repeated several times. The combined chloroform extracts were washed with dilute ammonia solution and with water, dried over anhydrous magnesium sulphate, and evaporated to dryness. The residue, after recrystallisation from ethyl alcohol (yield 5·9 g.; 49%), showed m. p. 206°, $[\alpha]_D^{12°}$ −28·9° in chloroform (*c*, 1·73). Schultz and Tollens (*loc. cit.*) record m. p. 206°, and $[\alpha]_D$ −29·3° (in chloroform) for trimethylene sorbitol.

The substance prepared in the above experiments was repeatedly recrystallised from ethyl alcohol and eventually showed m. p. 212—213°, $[\alpha]_D^{12°}$ −28·2° in chloroform (*c*, 6·32); it was therefore pure trimethylene sorbitol (Found: C, 50·0; H, 6·4. Calc. for $C_9H_{14}O_9$: C, 49·5; H, 6·4%).

Hydrolysis of Trimethylene Sorbitol.—(*a*) *By* 70% *acetic acid.* Trimethylene sorbitol (0·34 g.) (m. p. 206°) was heated with 20 c.c. of 70% acetic acid for 2½ hours at 100° without there being any perceptible change in the specific rotation of the solution. On evaporation, unchanged starting material was recovered.

(*b*) *By* N-*sulphuric acid.* Trimethylene sorbitol (1·818 g.) (m. p. 206°) was boiled with 30 c.c. of N-sulphuric acid for 2 hours, the specific rotation changing from $[\alpha]_D$ −30·0° to $[\alpha]_D$ −18·2° (constant value). The solution was neutralised with barium carbonate, filtered, and evaporated to dryness. The crystalline residue was extracted three times with hot chloroform, and the extract evaporated to dryness and recrystallised, forming feathery needles from

chloroform (0·53 g.). This substance was 1 : 3-2 : 4-*dimethylene sorbitol* and showed m. p. 173°, $[\alpha]_D^{18°}$ −25·6° in water (*c*, 6·33) (Found: C, 46·4; H, 6·7. $C_8H_{14}O_6$ requires C, 46·6; H, 6·8%). The material was extremely soluble in ethyl alcohol and water but not very soluble in chloroform.

The residue, after chloroform extraction, was extracted with hot ethyl alcohol. This extract was evaporated to 2 c.c. and a little ether added, whereupon feathery crystals of 2 : 4-*monomethylene sorbitol* separated and were recrystallised from ethyl alcohol–ether (yield 0·11 g.), m. p. 162°, $[\alpha]_D^{21°}$ −9·1° in water (*c*, 3·632) (Found: C, 43·7; H, 7·6. $C_7H_{14}O_6$ requires C, 43·3; H, 7·3%).

Remethylenation of 2 : 4-*Monomethylene Sorbitol.*—2 : 4-Monomethylene sorbitol (0·066 g.) was mixed with paraformaldehyde (0·15 g.), and the mixture warmed with concentrated sulphuric acid (0·2 c.c.) until a clear solution was obtained; it was then shaken for several hours with chloroform, the chloroform extract decanted, and the extraction process repeated twice more. The combined extracts were washed with dilute ammonia solution and with water, dried over anhydrous magnesium sulphate, and evaporated to dryness. The residue recrystallised from methyl alcohol in the form of needles, m. p. 209—210°, mixed m. p. with authentic pure trimethylene sorbitol 210—212°.

Remethylenation of 1 : 3-2 : 4-*Dimethylene Sorbitol.*—1 : 3-2 : 4-Dimethylene sorbitol (0·735 g.) was warmed with paraformaldehyde (1·5 g.) and concentrated sulphuric acid (1·0 c.c.) until a clear solution was obtained; this was then extracted several times with chloroform, the chloroform extract washed with dilute ammonia solution and with water, and evaporated to dryness. The residue, recrystallised from methyl alcohol (yield 0·230 g.), had m. p. 209—210°, undepressed on admixture with trimethylene sorbitol (m. p. 210—212°).

Monobenzoyl 1 : 3-2 : 4-*Dimethylene Sorbitol.*—1 : 3-2 : 4-Dimethylene sorbitol (1 g.) was dissolved in 5N-sodium hydroxide solution (10 c.c.), benzoyl chloride (2·5 c.c.) added, and the mixture shaken for several hours. The solid which separated was filtered off, washed with water, and recrystallised from alcohol. It was probably 6-*benzoyl* 1 : 3-2 : 4-*dimethylene sorbitol*. Yield, 0·6 g., m. p. 195—197°, $[\alpha]_D$ −15·9° in chloroform (*c*, 0·877) (Found: C, 58·4; H, 5·5. $C_{14}H_{18}O_7$ requires C, 58·1; H, 5·8%).

5 : 6-*Dibenzoyl* 1 : 3-2 : 4-*Dimethylene Sorbitol.*—1 : 3-2 : 4-Dimethylene sorbitol (1 g.) was dissolved in dry pyridine (20 c.c.), and benzoyl chloride (3·5 c.c.) added. The mixture became warm and pyridine hydrochloride separated; after being kept overnight, it was poured into ice-water, whereupon a syrupy precipitate separated, which crystallised after being washed with water and triturated with alcohol; recrystallised from alcohol, it formed plates (0·55 g.), m. p. 135—137° $[\alpha]_D^{18°}$ −56·3° in chloroform (*c*, 1·135) (Found: C, 63·7; H, 5·2. $C_{28}H_{28}O_8$ requires C, 63·8; H, 5·3%).

6-*Trityl* 1 : 3-2 : 4-*Dimethylene Sorbitol.*—1 : 3-2 : 4-Dimethylene sorbitol (0·27 g.) was dissolved in dry pyridine (3 c.c.), trityl chloride (1·1 mols.) added, and the mixture kept for 4 days at room temperature. On pouring this into water, a crystalline precipitate separated, which, after being washed with water, was recrystallised from alcohol (0·32 g.), m. p. 194°, $[\alpha]_D^{20°}$ −8·0° in chloroform (*c*, 2·0) (Found: C, 72·9; H, 6·2. $C_{27}H_{28}O_6$ requires C, 72·3; H, 6·3%).

5 : 6-*Diacetyl Dimethylene Sorbitol.*—Dimethylene sorbitol (0·3 g.) was boiled with acetic anhydride (5 c.c.) and fused sodium acetate (0·4 g.) for 5 minutes. The product was poured into ice-water, and after several hours the solution was neutralised with sodium hydrogen carbonate and extracted with chloroform. After being dried over magnesium sulphate, the extract was evaporated to dryness and the residue recrystallised from alcohol (0·33 g.), m. p. 135—136°, $[\alpha]_D^{18°}$ −15·4° in chloroform (*c*, 1·69) (Found: C, 49·4; H, 6·4; Ac, 30·1. $C_{12}H_{18}O_8$ requires C, 49·5; H, 6·2; Ac, 29·6%).

5 : 6-*Dimethyl* 1 : 3-2 : 4-*Dimethylene Sorbitol.*—Dimethylene sorbitol (1 g.) was methylated by means of silver oxide and methyl iodide in the usual manner. After three treatments the product was recrystallised from ethyl alcohol, forming lustrous needles (0·24 g.), m. p. 193—194°, $[\alpha]_D^{20°}$ −23·8° in chloroform (*c*, 0·587) (Found: C, 51·4; H, 7·7. $C_{10}H_{18}O_6$ requires C, 51·3; H, 7·7%).

5 : 6-*Dimethyl Dimethylene Sorbitol from* 1 : 2-3 : 4-*Diethylidene Sorbitol.*—5 : 6-*Dimethyl* 1 : 2-3 : 4-*diethylidene sorbitol.* Diethylidene sorbitol (3 g.), prepared by Appel's method (*loc. cit.*), was methylated by five treatments with silver oxide and methyl iodide, the product being extracted after each treatment with boiling chloroform. The methylation was difficult owing to the insolubility of diethylidene sorbitol. Finally a syrup was obtained which distilled at 140° (bath temp.)/0·03 mm. (1·25 g.), $n_D^{21°}$ 1·4616, $[\alpha]_D^{15°}$ −9·8° in chloroform (*c*, 2·555) (Found: C, 54·6; H, 8·1. $C_{12}H_{22}O_6$ requires C, 54·9; H, 8·4%).

Methylenation of 5 : 6-*dimethyl diethylidene sorbitol.* The foregoing 5 : 6-*dimethyl diethylidene sorbitol* (1·2 g.) was warmed for 20 minutes with paraformaldehyde (1·2 g.) and concentrated sulphuric acid (1 c.c.) during which the evolution of acetaldehyde occurred. The mixture was then shaken with chloroform for 3 hours, the chloroform decanted, and the operation repeated. The combined chloroform extracts were washed with sodium bicarbonate solution and with water, dried over anhydrous magnesium sulphate, and evaporated to dryness. The residue recrystallised from alcohol in lustrous needles of 5 : 6-dimethyl 1 : 3-2 : 4-dimethylene sorbitol (0·25 g.), m. p. 193—194°, $[\alpha]_D$ −22·2° in chloroform (*c*, 0·678) (Found: C, 51·6; H, 8·0%); the mixed m. p. with the specimen prepared as above showed no depression.

1 : 6-*Ditosyl* 2 : 4-*Monomethylene Sorbitol.*—2 : 4-Monomethylene sorbitol (0·3 g.) was dissolved in dry pyridine (3 c.c.), and tosyl chloride (0·6 g.) added in small portions at 0°. The solution was allowed to warm to room temperature, and kept thereat for 24 hours. On pouring into ice-water a syrup was precipitated which rapidly crystallised. The crystals were collected, washed with water, and recrystallised from alcohol, affording feathery needles (0·31 g.), m. p. 129—130°, $[\alpha]_D^{18°}$ −2·0° in chloroform (*c*, 2·0) (Found: C, 49·7; H, 5·2. $C_{21}H_{26}O_{10}S_2$ requires C, 50·2; H, 5·2%).

Treatment of 1 : 6-*Ditosyl* 2 : 4-*Monomethylene Sorbitol with Sodium Iodide in Acetone Solution.*—A solution of this 1 : 6-*ditosyl* 2 : 4-*monomethylene sorbitol* (0·3 g.) and dry sodium iodide (0·7 g.) in dry acetone (50 c.c.) was heated in a sealed tube at 110° for 8 hours. Crystals of sodium *p*-toluenesulphonate separated during the reaction. When the tube had cooled, these crystals were filtered off and weighed (0·205 g.; 80%). The acetone filtrate was evaporated, and the residue treated with a chloroform–water mixture. A little sodium thiosulphate was added, and the mixture shaken in a separating funnel. Some material would not dissolve in either layer; this was collected and recrystallised from alcohol, forming plates (0·12 g.), m. p. 210° (Found: C, 20·9; H, 3·4; I, 59·3. $C_7H_{12}O_4I_2$ requires C, 20·4; H, 3·0; I, 61·3%). It was 1 : 6-*di-iodo monomethylene sorbitol.* The chloroform layer of the filtrate from these crystals was separated, washed with water, dried over anhydrous magnesium sulphate, and evaporated to dryness. The residue recrystallised from alcohol in feathery needles (0·18 g.), m. p. 185° (Found: C, 32·2; H, 4·1; I, 36·4%). This substance has not been identified.

Benzoylation of 2 : 4-*Monomethylene Sorbitol.*—2 : 4-Monomethylene sorbitol (0·18 g.) was dissolved in dilute sodium hydroxide solution, benzoyl chloride (0·44 c.c.) added, and the mixture shaken for several hours and diluted with ice-water. The precipitate was filtered off and recrystallised twice from ethyl alcohol (0·03 g.), m. p. 154°, $[\alpha]_D^{20°}$ −10·0° in chloroform (*c*, 0·4) (Found: C, 66·5; H, 5·2. $C_{28}H_{26}O_8$ requires C, 66·4; H, 5·2%); it was *tribenzoyl monomethylene sorbitol.* Benzoylation in pyridine solution gave only a syrupy product which resisted attempts at crystallisation.

1 : 6-*Ditrityl* 2 : 4-*Monomethylene Sorbitol.*—2 : 4-Monomethylene sorbitol (0·49 g.) was dissolved in dry pyridine (5 c.c.), trityl chloride (2·2 mols.) added, and the mixture set aside for 24 hours. On pouring this into water, a syrupy precipitate separated which was triturated with water and then dissolved in chloroform. The chloroform extract was washed with 5% sulphuric acid, with dilute sodium bicarbonate, and with water, dried over anhydrous magnesium

sulphate, and evaporated. A syrup was left which crystallised after several weeks. It was recrystallised with difficulty from pyridine; m. p. 112—115° (Found: C, 79·9; H, 6·5. $C_{45}H_{40}O_6$ requires C, 79·8; H, 6·0%). An attempt to tritylate and then acetylate monomethylene sorbitol in the same pyridine solution gave only *tetra-acetyl 2:4-monomethylene sorbitol*, m. p. 152°, $[\alpha]_D$ −4·0° in chloroform (*c*, 1·5) (Found: C, 50·1; H, 6·2; Ac, 48·4. $C_{15}H_{22}O_{10}$ requires C, 49·7; H, 6·1; Ac, 47·5%).

Oxidation of Dimethylene Sorbitol with Lead Tetra-acetate and with Bromine.—Dimethylene sorbitol (1·84 g.) was dissolved in glacial acetic acid (40 c.c.), lead tetra-acetate (1·2 mols.) added, and the mixture shaken for 24 hours. After evaporating it to dryness at 30°/15 mm., water was added, and the mixture again evaporated in order to remove the last traces of acetic acid. The residue was dissolved in water (20 c.c.), excess of bromine (4 c.c.) added, and the mixture kept at 30° for 4 days. The excess bromine was removed by aeration, and the lead bromide precipitate (A) filtered off. The filtrate was neutralised with lead carbonate and filtered, the residue (B) was washed well with water, and the combined filtrate and washings evaporated to a syrup which was refluxed with 5% methyl-alcoholic hydrogen chloride (200 c.c.) for 6 hours. The alcoholic solution was neutralised with lead carbonate, filtered, and evaporated to dryness; the residue recrystallised from methyl alcohol in small needles (0·042 g.), m. p. 195°. A further amount was obtained from the lead carbonate residue (B) by repeated extraction with boiling water (the lead salt of the dimethylene pentonic acid was only slightly soluble in water). The aqueous extract was evaporated to dryness, the lead bromide precipitate (A) added to the product, and the mixture refluxed with 4% methyl-alcoholic hydrogen chloride (300 c.c.) for 6 hours. After neutralisation with lead carbonate, filtration, and evaporation, the residue was recrystallised twice from methyl alcohol. Total yield, 0·432 g. (23·5%), m. p. 200°, $[\alpha]_D^{18°}$ −33·0° in chloroform (*c*, 1·076) (Found: C, 46·8; H, 6·0. $C_6H_{12}O_6$ requires C, 47·1; H, 5·9%). This substance was *methyl dimethylene* l-*xylonate*.

Dimethylene l-*Xylonamide*.—The foregoing ester (45 mg.) was dissolved in dry methyl alcohol (5 c.c.), the solution saturated with ammonia at 0°, and kept for 24 hours. Evaporation in a vacuum gave a mass of crystals which was recrystallised from methyl alcohol (30 mg.), m. p. 267° (Found: C, 44·7; H, 5·6. $C_7H_{11}O_5N$ requires C, 44·4; H, 5·8%).

Methyl Dimethylene d-*Arabonate*.—*d*-Arabinose was oxidised by means of bromine water in the usual way, and the resulting syrupy arabonic acid–lactone mixture (1 g.) methylenated by gentle warming with paraformaldehyde (1 g.) and concentrated sulphuric acid (0·8 c.c.) for 15 minutes. The mixture was then refluxed for 6 hours with methyl alcohol (100 c.c.), and after neutralisation of the sulphuric acid with barium carbonate, the filtered solution was evaporated to dryness. Upon extraction with chloroform and subsequent removal of the solvent, a syrup was obtained which partly crystallised. This was recrystallised to give *methyl dimethylene* d-*arabonate* (0·10 g.), m. p. 200—201°, $[\alpha]_D$ −31·1° in chloroform (*c*, 3·540) (Found: C, 47·0; H, 6·2. $C_6H_{12}O_6$ requires C, 47·1; H, 5·9%). From the mother-liquors was isolated 0·06 g. of an isomeric *ester*, m. p. 99—100°, $[\alpha]_D^{18°}$ −75·2° in chloroform (*c*, 1·01) (Found: C, 47·4; H, 6·2%). In a second preparation, however, we failed to obtain any of this isomer.

Dimethylene d-*Arabonamide*.—Methyl dimethylene *d*-arabonate (0·13 g.) was suspended in dry methyl alcohol (5 c.c.), the mixture saturated with ammonia at 0°, and the solution kept at 0° for 24 hours, during which time some feathery needles crystallised. The mixture was evaporated in a vacuum, and the residue recrystallised from methyl alcohol (90 mg.); m. p. 268° (Found: C, 43·9; H, 5·6. $C_7H_{11}O_5N$ requires C, 44·4; H, 5·8%).

Methyl Dimethylene l-*Arabonate*.—This *ester* was prepared from *l*-arabinose in the same way as the enantiomorphic compound from *d*-arabinose. It had m. p. 200—201°; $[\alpha]_D^{18°}$ +34·1° in chloroform (*c*, 1·35) (Found: C, 47·2; H, 5·8. $C_6H_{12}O_6$ requires C, 47·0; H, 5·9%). No isomeric ester was found.

Dimethylene l-*Arabonamide*.—This *amide* was prepared in the same way as its enantiomorph and had m. p. 268° (Found: C, 44·7; H, 5·9. $C_7H_{11}O_5N$ requires C, 44·4; H, 5·8%).

Methyl Dimethylene d-*Xylonate*.—*d*-Xylose was oxidised by means of bromine water in the usual way. The syrupy xylonic acid–lactone mixture (1·02 g.) was methylenated by warming with paraformaldehyde (1 g.) and concentrated sulphuric acid (3 c.c.) until a clear solution was obtained. Methyl alcohol (80 c.c.) was then added, and the solution boiled for 6 hours. Thereafter it was neutralised with barium carbonate, filtered, evaporated to dryness, and the residue extracted with chloroform. This extract, on evaporation, gave a crystalline residue which recrystallised from methyl alcohol in long feathery needles (0·11 g.), m. p. 200°, $[\alpha]_D^{22°}$ +32·0° in chloroform (*c*, 3·0) (Found: C, 47·1; H, 5·7. $C_6H_{12}O_6$ requires C, 47·0; H, 5·9%).

Dimethylene d-*Xylonamide*.—The foregoing *ester* (30 mg.) was dissolved in dry methyl alcohol (5 c.c.), the solution saturated with ammonia gas at 0°, and kept at that temperature for 24 hours; the solvent and the ammonia were removed in a vacuum, and the residue recrystallised from methyl alcohol, forming feathery needles (15 mg.), m. p. 267° (Found: C, 44·0; H, 5·6. $C_7H_{11}O_5N$ requires C, 44·4; H, 5·8%).

Oxidation-rate Determinations with Lead Tetra-acetate.—The procedure used was that of Hockett and McClenahan (*loc. cit.*). 0·0005 Mol. of the substance to be oxidised was dissolved in glacial acetic acid (49 c.c.) in a 100-c.c. flask, and lead tetra-acetate solution (50 c.c.) (15 g. in 500 c.c. of glacial acetic acid) rapidly run in; the volume was made up to 100 c.c. with glacial acetic acid, and the solution thoroughly shaken. A 10-c.c. sample was withdrawn as quickly as possible after the oxidising agent had been added, and run into potassium iodide–sodium acetate solution (20 c.c.) [potassium iodide (10 g.) and crystalline sodium acetate (125 g.) in water (500 c.c.)], the liberated iodine being titrated with 0·02N-sodium thiosulphate. At intervals, further 10-c.c. portions were withdrawn, and the amount of oxidising agent consumed estimated. A blank titration was carried out with 5 c.c. of the standard lead tetra-acetate just beforehand. From these data the number of g.-atoms of oxygen taken up by 1 g.-mol. of the compound used could be calculated:

(*a*) Dimethylene sorbitol (0·1021 g.); 0·11 (3 mins.); 0·38 (15 mins.); 0·78 (48 mins.); 0·94 (84 mins.); 0·98 (112 mins.); 1·02 (156 mins.). (*b*) Diethylidene sorbitol (0·108 g.): 0·13 (4 mins.); 0·56 (25 mins.); 0·74 (41 mins.); 0·87 (65 mins.); 0·93 (108 mins.); 1·02 (720 mins.). (*c*) 2:4-Monomethylene sorbitol (0·095 g.): 0·10 (3 mins.); 0·51 (23 mins.); 0·78 (56 mins.); 0·86 (78 mins.); 0·95 (130 mins.); 1·12 (750 mins.). (*d*) 3:4-Monoacetone mannitol (0·111 g.): 0·20 (3 mins.); 0·96 (35 mins.); 1·46 (88 mins.); 1·98 (247 mins.). (*e*) 1:6-Ditosyl 2:4-monomethylene sorbitol (0·260 g.): 0·06 (3 mins.); 0·03 (21 mins.); 0·04 (60 mins.); 0·05 (111 mins.); 0·10 (230 mins.).

These results are shown graphically in the figure.

The authors wish to express their thanks to Professor W. N. Haworth, F.R.S., for his interest in this work, to Dr. S. Peat for valuable criticism and advice, and to Miss H. Daniels for assistance with the preparative work.

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[*Received, June 5th*, 1944.]

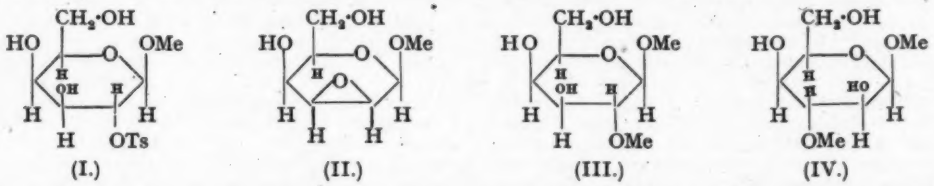
143. *The Conversion of Galactose into Derivatives of* d-*Idose.*

By L. F. Wiggins.

Galactose has been converted into *d*-idose derivatives through the intermediate formation of 4 : 6-benzylidene 2 : 3-anhydro-β-methyltaloside, obtained by alkaline hydrolysis of 2-tosyl 4 : 6-benzylidene β-methylgalactoside. It was observed that 2-tosyl 4 : 6-benzylidene α-methylgalactoside was considerably more stable to alkaline reagents than was the corresponding compound in the β-series. The anhydro-compound suffered ring fission to give 2-methyl 4 : 6-benzylidene β-methylgalactoside and 3-methyl 4 : 6-benzylidene β-methyl-*d*-idoside, the latter greatly predominating. Its formulation as a derivative of *d*-idose is proved by its conversion into the known crystalline tetramethyl δ-idonolactone. Fission of the anhydro-ring with ammonia led to the isolation of 3-acetamido 2-acetyl 4 : 6-benzylidene β-methyl-*d*-idoside but no 2-acetamido 3-acetyl 4 : 6-benzylidene β-methylgalactoside could be separated. Direct treatment of 2-tosyl 3 : 4 : 6-trimethyl β-methylgalactoside with methyl-alcoholic ammonia led to the isolation of a very small amount of a substance believed to be 2-acetamido 3 : 4 : 6-trimethyl β-methylgalactoside.

In the course of an investigation designed to elucidate the configuration of the 2-aminohexose, chondrosamine, the synthesis of derivatives of 2-aminogalactose has been attempted by the procedure successfully employed by Haworth, Lake, and Peat (J., 1939, 271) in the determination of the constitution of glucosamine. The application of this method for the preparation of 2-aminogalactose necessitated the fission with ammonia of the ethylene oxide ring of a 2 : 3-anhydro-talose derivative, it having been shown (Peat and Wiggins, J., 1938, 1810) that such ethylene oxide anhydro-rings open in both of the possible directions with the production of two amino-sugars. In the present case 2 : 3-anhydrotalose would be expected to yield 2-aminogalactose and 3-aminoidose. It has been found possible to prepare a derivative of 2 : 3-anhydrotalose and to prove that it has the talose configuration. However, it was not possible to isolate the aminogalactose component of the products of ring scission with ammonia. Nevertheless it is noteworthy that a number of *d*-idose derivatives have been prepared, and evidence obtained which lends further experimental support to the theory of the mechanism of ring closure and ring scission in the anhydro-sugar group (cf. *Ann. Reports*, 1939, **36**, 258).

If this theory is generally applicable, then the following sequence is to be expected: 2-tosyl β-methylgalactoside (I) $\xrightarrow{\text{NaOMe}}$ 2 : 3-*anhydro*-β-*methyltaloside* (II) $\xrightarrow{\text{NaOMe}}$ 2-methyl β-methylgalactoside (III) + 3-*methyl* β-*methylidoside* (IV). Proof has been obtained that the products (III) and (IV) have in fact the configuration



(I.) (II.) (III.) (IV.)

of *d*-galactose and *d*-idose respectively, and in consequence this has provided further support for the hypothesis that Walden inversion accompanies the formation and the scission of ethylene oxide linkages in the sugars.

Crystalline 2 : 3-anhydro-β-methyltaloside was obtained when 2-tosyl β-methylgalactoside was detosylated. Treatment of the anhydro-methyltaloside with benzaldehyde yielded crystalline 4 : 6-*benzylidene* 2 : 3-*anhydro*-β-*methyltaloside* which was also obtained by detosylation of 2-*tosyl* 4 : 6-*benzylidene* β-*methylgalactoside*. When the anhydro-ring of the benzylidene 2 : 3-anhydro-β-methyltaloside was opened with sodium methoxide, two crystalline benzylidene β-methylhexosides, (A) and (B), were isolated. The compound (A), which was present in exceedingly small amount, was shown to be 2-methyl 4 : 6-benzylidene β-methylgalactoside inasmuch as no depression of melting point was observed in admixture with an authentic specimen prepared by Bell and Williamson's method (J., 1938, 1196). The main product (B), obtained in 64% yield, was shown to be 3-*methyl* 4 : 6-*benzylidene* β-*methylidoside*. The benzylidene group was removed from (B) by mild acid hydrolysis (see Robertson and Dunlop, J., 1938, 472), and the liquid monomethyl β-methylhexoside so obtained was methylated to a tetramethyl β-methylhexoside. The constants of this substance agreed closely with those given by Lake and Peat (J., 1939, 1069) for tetramethyl β-methyl-*d*-idoside. Hydrolysis gave a tetramethyl hexose, purified by distillation under high vacuum; subsequent oxidation yielded a crystalline tetramethyl hexonolactone shown to be identical with Lake and Peat's tetramethyl δ-idonolactone (*loc. cit.*). During the distillation of the tetramethyl idose, the octamethyl di-idose isolated by Lake and Peat was not encountered. The substance (B) therefore has the configuration of *d*-idose. It is clear that the methyl group of (B) must be located on either C_2 or C_3. The monomethyl β-methylidoside obtained from (B) was hydrolysed to monomethyl idose which was oxidised to monomethyl idonolactone. These products were non-crystalline. Treatment of the lactone with ammonia, however, yielded an amide which gave a positive Weerman test for α-hydroxyamides. The methyl group is therefore located on C_3, and (B) is correctly described as 3-methyl 4 : 6-benzylidene β-methylidoside, and the anhydro-methylhexoside from which it was derived as 4 : 6-benzylidene 2 : 3-anhydro-β-methyltaloside. Methylation of (B) yielded crystalline 2 : 3-*dimethyl* 4 : 6-*benzylidene* β-*methylidoside*.

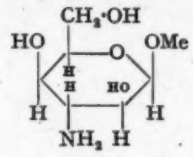
An alternative method of preparation consisted in the hydrolysis, with boiling methyl-alcoholic sodium methoxide, of 2 : 3-ditosyl 4 : 6-benzylidene β-methylgalactoside, prepared by the method of Bacon, Bell,

and Lorber (J., 1940, 1147). A little 4 : 6-benzylidene 2 : 3-anhydro-β-methyltaloside was isolated but, in the main, ring fission occurred and the product (B) was obtained together with a small amount of (A).

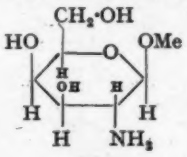
Methylation of 2 : 3-anhydro-β-methyltaloside gave 4 : 6-*dimethyl* 2 : 3-*anhydro*-β-*methyltaloside*, treatment of which with sodium methoxide yielded a trimethyl β-methylhexoside which, by analogy, is described as 3 : 4 : 6-*trimethyl* β-*methylidoside*, containing a trace of 2 : 4 : 6-trimethyl β-methylgalactoside. The product, however, was not crystalline.

An observation of considerable theoretical interest was made when the above series of reactions was carried out with the α-form of 2-tosyl methylgalactoside. Crystalline 2-*tosyl* 4 : 6-*benzylidene* α-*methylgalactoside* was prepared according to the following scheme: 3 : 4-monoacetone α-methylgalactoside ⟶ 6-trityl 3 : 4-monoacetone α-methylgalactoside ⟶ 6-trityl 2-tosyl 3 : 4-monoacetone α-methylgalactoside ⟶ 2-tosyl α-methylgalactoside ⟶ 2-tosyl 4 : 6-benzylidene α-methylgalactoside, the 3-*methyl* derivative of which was readily formed. 2-Tosyl 4 : 6-benzylidene α-methylgalactoside was distinguished by its extreme stability towards alkali: whereas its β-methyl analogue is detosylated by contact with cold sodium methoxide for 10 minutes, yet the α-isomer is not affected by boiling methyl-alcoholic sodium methoxide, and in order to remove the tosyl group it was necessary to heat the α-compound with the alkaline reagent at 120° for 20 hours. Presumably the 2 : 3-anhydrotalose derivative was first formed, but under these drastic conditions the anhydro-ring was immediately opened again and 3-*methyl* 4 : 6-*benzylidene* α-*methylidoside* was the only product obtained. The last compound was easily methylated to the 2 : 3-*dimethyl* homologue. A similar, though not precisely analogous, case was noted by Percival and Percival (J., 1938, 1585), who found that 3-tosyl 2 : 4 : 6-trimethyl α-methylgalactoside, in contrast to the corresponding β-form, was extremely resistant to alkaline hydrolysis.

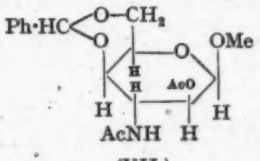
The action of methyl-alcoholic ammonia on 2 : 3-anhydro-β-methyltaloside was next investigated. The main product of this reaction was a crystalline amino-sugar which, by analogy with work on the action of sodium methoxide on the anhydro-compound, was 3-*amino*-β-*methyl*-d-*idoside* (V). It was accompanied by a syrupy product of different specific rotation, which presumably contained 2-amino-β-methylgalactoside (VI): none, however, was isolated in solid form. The 3-amino-β-methylidoside gave crystalline 3-*acetamido* 2 : 4 : 6-*triacetyl* β-*methyl*-d-*idoside* and also 3-*acetamido* β-*methyl*-d-*idoside*.



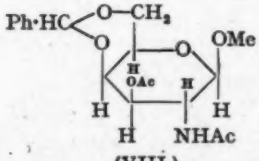
(V.)



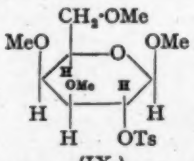
(VI.)



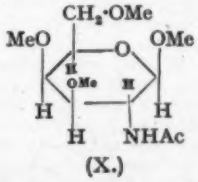
(VII.)



(VIII.)



(IX.)



(X.)

Similarly, only one crystalline compound was isolated by the action of ammonia on 4 : 6-benzylidene 2 : 3-anhydro-β-methyltaloside, followed by acetylation. This was 3-*acetamido* 2-*acetyl* 4 : 6-*benzylidene* β-*methyl*-d-*idoside* (VII). 2-Acetamido 3-acetyl 4 : 6-benzylidene β-methylgalactoside (VIII) should be present in the residual syrups, but so far it has not been possible to crystallise it.

A further attempt was made to obtain a derivative of 2-aminogalactose by treatment of 2-*tosyl* 3 : 4 : 6-*trimethyl* β-*methylgalactoside* (IX) with methyl-alcoholic ammonia, for by this procedure from the corresponding glucose derivative Cutler and Peat (J., 1939, 782) obtained 2-acetamido 3 : 4 : 6-trimethyl β-methylglucoside in very small yield. By adopting this procedure, a very small amount of a crystalline product was isolated, but in insufficient quantity for analyses. By analogy with the work in the glucosamine series, the compound was probably 2-acetamido 3 : 4 : 6-trimethyl β-methylgalactoside (X). It showed m. p. 238°, which is near to the value given for 2-acetyl 3 : 4 : 6-trimethyl β-methylchondrosaminide by Stacey (this vol., p. 274), *viz.*, m. p. 233°. However, on admixture with a sample of this compound prepared from chondrosamine by Dr. M. Stacey of this department, the m. p. was depressed to 226—228°. A parallel experiment with the corresponding compound in the α-series failed altogether to give any crystalline amino-derivative.

It is to be noted that, whereas in the case of ring opening of 4 : 6-benzylidene 2 : 3-anhydro-α-methylalloside with sodium methoxide (Peat and Wiggins, *loc. cit.*) the second product, *viz.*, 3-methyl 4 : 6-benzylidene α-methylglucoside, was isolated quite easily and in 10% yield, in the present case the second product from the sodium methoxide ring fission, *viz.*, 2-methyl 4 : 6-benzylidene β-methylgalactoside, was isolated with the utmost difficulty and in minute yield, a fact which most probably contributes to the lack of success in isolating a corresponding amino-compound by the ring fission with ammonia.

Experimental.

2 : 3-*Anhydro*-β-*methyl*-d-*taloside*.—2-Tosyl β-methylgalactoside (0·6 g.), prepared according to the procedure of Bacon, Bell, and Kosterlitz (J., 1939, 1248), was dissolved in dry methyl alcohol (10 c.c.), and 10% sodium methoxide solution

in methyl alcohol (1·2 c.c.) added. The mixture was kept for 24 hours at room temperature, and the excess sodium methoxide neutralised with N-sulphuric acid. The solution was evaporated to dryness under reduced pressure, and the residue extracted with ethyl acetate. Evaporation of the extract gave a semi-crystalline mass which, recrystallised from ethyl acetate, formed long rods (0·21 g.). There was a residual syrup which could not be crystallised; m. p. 103—104°, $[\alpha]_D^{17°}$ −86·1° in chloroform (*c*, 1·02) (Found: C, 48·1; H, 6·5; OMe, 18·2. $C_7H_{12}O_5$ requires C, 47·7; H, 6·8; OMe, 17·6%).

4 : 6-*Benzylidene* 2 : 3-*Anhydro-β-methyl*-d-*taloside*.—The foregoing 2 : 3-*anhydro-β-methyl*-d-*taloside* (80 mg.) was shaken with freshly distilled benzaldehyde (2 c.c.) and anhydrous zinc chloride (0·5 g.) for 24 hours. Excess of sodium carbonate solution was added, and the excess benzaldehyde removed by distillation with steam. After evaporation to dryness the residue was extracted several times with boiling chloroform. On evaporation of the extract, a crystalline residue was obtained which recrystallised from chloroform–light petroleum, forming long needles (50 mg.), m. p. 242°, $[\alpha]_D^{19°}$ −138·4° in chloroform (*c*, 0·578) (Found: C, 63·2; H, 6·1; OMe, 12·2. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1; OMe, 11·8%).

4 : 6-*Dimethyl* 2 : 3-*Anhydro-β-methyl*-d-*taloside*.—2 : 3-Anhydro-β-methyl-*d*-taloside (0·5 g.) was treated three times with methyl iodide and dry silver oxide at 45°, the product being extracted with boiling chloroform after each treatment. The product finally obtained was recrystallised from ether–light petroleum, forming fine, long needles (0·4 g.), m. p. 72—73°, $[\alpha]_D^{18°}$ −148·4° in chloroform (*c*, 0·89) (Found: C, 53·1; H, 7·8; OMe, 45·6. $C_9H_{16}O_5$ requires C, 52·9; H, 7·8; OMe, 45·6%).

2-*Tosyl* 4 : 6-*Benzylidene β-Methylgalactoside*.—2-Tosyl β-methylgalactoside (7 g.) was shaken with freshly distilled benzaldehyde (30 c.c.) and pulverised anhydrous zinc chloride (10 g.) for 4 hours. The calculated quantity of sodium carbonate, dissolved in water, was added, and the excess benzaldehyde steam-distilled. After evaporation to dryness, the residue was extracted with chloroform. The syrup obtained on evaporation of the extraction liquid crystallised on trituration with alcohol and ether. After recrystallisation from alcohol, 2-*tosyl* 4 : 6-*benzylidene β-methylgalactoside* (6 g.) showed m. p. 164—165°, $[\alpha]_D^{17°}$ −52·8° in chloroform (*c*, 2·388) (Found: C, 57·7; H, 5·7. $C_{21}H_{24}O_8S$ requires C, 57·8; H, 5·5%).

Detosylation of 2-*Tosyl* 4 : 6-*Benzylidene β-Methylgalactoside*.—The galactoside (5·7 g.) was dissolved in chloroform (50 c.c.), and a slight excess of methyl-alcoholic sodium methoxide solution (6 c.c., 1 c.c. = 0·136 g. of sodium methoxide) added. The mixture was vigorously shaken for about 15 minutes, during which the solution became gelatinous and finally a crystalline precipitate consisting of sodium *p*-toluenesulphonate and 4 : 6-benzylidene 2 : 3-anhydro-β-methyl-*d*-taloside separated. The solution was then set aside for 24 hours, filtered, the precipitate washed with water to remove the sodium salt, and recrystallised from chloroform–light petroleum. The product formed large feathery needles (m. p. 242°) and was identical with the 4 : 6-benzylidene 2 : 3-anhydro-β-methyltaloside obtained by benzylidenation of the 2 : 3-anhydro-β-methyl-*d*-taloside. An additional amount was obtained from the initial chloroform filtrate from the crystalline reaction product. The chloroform solution was washed with water, dried over anhydrous magnesium sulphate, filtered, and evaporated to dryness, the residue being recrystallised from chloroform–petrol; m. p. 242°. The total yield of the anhydro-compound was 2·65 g. (78%).

2 : 3-*Ditosyl* 4 : 6-*Benzylidene β-Methylgalactoside*.—4 : 6-Benzylidene β-methylgalactoside (29 g.) was dissolved in pyridine (150 c.c.), and tosyl chloride (42 g.) added with cooling. After the addition was complete, the mixture was warmed at 40° for 4 days, and poured into ice-water; the syrupy precipitate obtained crystallised on trituration with water and alcohol. 2 : 3-Ditosyl 4 : 6-benzylidene β-methylgalactoside separated from ethyl alcohol (28 g.), m. p. 169—171°, $[\alpha]_D^{20°}$ +27·4° in chloroform (*c*, 1·24) (Found: C, 57·3; H, 5·0. Calc. for $C_{28}H_{30}O_{10}S_2$: C, 57·0; H, 5·1%). Bacon, Bell, and Lorber (J., 1940, 1147) give m. p. 168—170°, $[\alpha]_D$ +29·5° in chloroform.

Alkaline Hydrolysis of 2 : 3-*Ditosyl* 4 : 6-*Benzylidene β-Methylgalactoside*.—The galactoside (27 g.) was heated with dry methyl alcohol (120 c.c.) containing sodium (3·6 g., 2 mols.) under reflux for 7 hours, solution then being complete. No crystals separated on cooling, and the solution was diluted with water and exhaustively extracted with chloroform. The extract on evaporation gave a syrup (10·5 g.) which was fractionally crystallised from alcohol. The first fraction (0·5 g.) showed m. p. 242° after recrystallisation and was 4 : 6-benzylidene 2 : 3-anhydro-β-methyl-*d*-taloside. Unchanged galactoside (2·3 g.) was next encountered, and the third fraction (4·4 g.), m. p. 105°, was identical with 3-methyl 4 : 6-benzylidene β-methyl-*d*-taloside (see below). A fourth and last fraction (0·15 g.) showed $[\alpha]_D$ −31·2° in chloroform (*c*, 1·67), m. p. 159—160° unchanged by admixture with 2-methyl 4 : 6-benzylidene β-methylgalactoside, which was described (Bell and Williamson, J., 1938, 1196) as having m. p. 160° and $[\alpha]_D$ −32·8° in chloroform. There was a residual syrup which would not yield any further crystals.

Hydrolysis of 4 : 6-*Benzylidene* 2 : 3-*Anhydro-β-methyl*-d-*taloside with Sodium Methoxide*.—The taloside (1 g.) was heated under reflux for 24 hours with 50 c.c. of dry methyl alcohol and 10 c.c. of 5% methyl-alcoholic sodium methoxide solution. The solution was diluted with water and exhaustively extracted with chloroform. The extract was dried over anhydrous magnesium sulphate, filtered, and evaporated to give a syrup (0·95 g.) which crystallised on trituration with ether. Fractional recrystallisation gave 3-*methyl* 4 : 6-*benzylidene β-methyl*-d-*idoside* (0·71 g.; 64%), m. p. 105°, $[\alpha]_D^{22°}$ −78·5° in chloroform (*c*, 1·325) (Found: C, 60·7; H, 6·7; OMe, 20·5. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·7; OMe, 20·9%), and a syrupy residue which, with great difficulty, was made to deposit a few crystals of 2-methyl 4 : 6-benzylidene β-methyl-galactoside (0·003 g.; 0·27% of the theoretical), m. p. and mixed m. p. with an authentic specimen 159—160°.

2 : 3-*Dimethyl* 4 : 6-*Benzylidene β-Methyl*-d-*idoside*.—3-Methyl 4 : 6-benzylidene β-methyl-*d*-iodside (40 mg.) was methylated by three treatments with methyl iodide and dry silver oxide, the product being extracted after each treatment 6 times with boiling chloroform. The final product was recrystallised from ether–light petroleum and showed m. p. 127°, $[\alpha]_D^{21°}$ −53·2° in chloroform (*c*, 0·601); yield, 30 mg. (Found: C, 61·5; H, 7·1; OMe, 30·4. $C_{16}H_{22}O_6$ requires C, 61·9; H, 7·1; OMe, 30·0%).

Partial Hydrolysis of 3-*Methyl* 4 : 6-*Benzylidene β-Methyl*-d-*idoside*.—3-Methyl 4 : 6-benzylidene β-methyl-*d*-idoside (3·5 g.) was dissolved in acetone (200 c.c.), oxalic acid (10 g.) dissolved in water (35 c.c.) added, and the mixture heated under reflux for 11½ hours. The specific rotation changed from $[\alpha]_D$ −84·8° to −53·4° (constant value) in 8½ hours. The acid was then neutralised with barium carbonate, the solution filtered, and the filtrate and washings evaporated to dryness. The residue was extracted with ethyl acetate, evaporation of which gave a syrup (2·1 g.) (Found: OMe, 28·8. $C_9H_{16}O_6$ requires OMe, 29·8%). The syrup could not be induced to crystallise, but was certainly 3-*methyl β-methyl*-d-*idoside*. A sample (0·2 g.) was rebenzylidenated by treating it with benzaldehyde (3 c.c.) and zinc chloride (0·5 g.) in the usual way. 3-Methyl 4 : 6-benzylidene β-methyl-*d*-idoside (0·17 g.), m. p. 105°, was obtained.

Tetramethyl β-Methyl-d-*idoside*.—3-Methyl β-methyl-*d*-idoside (0·6 g.) was methylated by four treatments with methyl iodide and silver oxide, the product being extracted after each treatment several times with boiling chloroform. The final product was distilled at 90—100°/0·03 mm. (bath temp.) (Found: OMe, 61·2. Calc. for $C_{11}H_{22}O_6$: OMe, 62·0%); yield, 0·5 g., $n_D^{19°}$ 1·4500, $[\alpha]_D^{18°}$ −67·7° in chloroform (*c*, 1·24). Lake and Peat (*loc. cit.*) record $[\alpha]_D$ −68·5° in chloroform, $n_D^{19°}$ 1·4490.

Tetramethyl d-*Idose*.—Tetramethyl β-methyl-*d*-idoside (0·48 g.) was heated in N-sulphuric acid (25 c.c.) at 100° for 5 hours: $[\alpha]_D$ −45·3° (initial value); +13·5° (½ hr.); +19·7° (1½ hrs.); +19·7° (5 hrs.). The acid was neutralised with

barium carbonate, the solution filtered, washed with water, and the combined filtrate and washings evaporated to dryness. The dry residue was repeatedly extracted with boiling chloroform, and on evaporation, the extract gave a syrup which distilled completely at 150—160° (bath temp.)/0·07 mm.; yield, 0·32 g., $n_D^{16°}$ 1·4616, $[\alpha]_D^{15°}$ +18·6° in methyl alcohol (*c*, 1·448) (Found: OMe, 51·6. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%). Lake and Peat (*loc. cit.*) gave $n_D^{15°}$ 1·4620, $[\alpha]_D$ +21·8° in methyl alcohol. No disaccharide such as that described by Lake and Peat was encountered.

Tetramethyl δ-Idonolactone.—Tetramethyl *d*-idose (0·2 g.) was dissolved in water (3 c.c.), bromine (1 c.c.) added, and the mixture kept at room temperature, with occasional shaking, for a week. The oxidation product was isolated in the usual way, and a syrup (0·13 g.) obtained which crystallised on trituration with ether. Recrystallised from ether, the product formed large prisms, m. p. 88—90°, unchanged in admixture with a specimen obtained by Lake and Peat (*loc. cit.*) and having $[\alpha]_D^{22°}$ −29·7° in water (*c*, 0·672) (no change after 72 hrs.) (Found: C, 51·4; H, 7·5. Calc. for $C_{10}H_{18}O_6$: C, 51·3; H, 7·5%). Lake and Peat (*loc. cit.*) describe tetramethyl δ-idonolactone as showing m. p. 91° and $[\alpha]_D$ −32·0° in water, and no change in rotation on keeping for 72 hours.

3-*Methyl* d-*Idose.*—3-Methyl β-methylidoside (0·18 g.) was heated with N-sulphuric acid (15 c.c.) for 10 hours at 95°, $[\alpha]_D$ −43·3° (initial value); −1·67° (½ hr.); −26·7° (1½ hrs.); −41·6° (3 hrs.); −56·6° (5½ hrs.); −53·3° (8 hrs.); −54·9° (10 hrs.). The solution, which now reduced Fehling's solution, was neutralised with barium carbonate, filtered, the precipitate washed with hot water, and the filtrate evaporated to dryness. On extracting the residue with absolute alcohol and evaporating the extract, syrupy 3-methyl *d*-idose was obtained (0·13 g.), $[\alpha]_D^{22°}$ −44·5° in water (*c*, 1·241) (Found: OMe, 17·0. Calc. for $C_7H_{14}O_6$: OMe, 16·0%).

3-*Methyl* d-*Idonamide.*—3-Methyl *d*-idose (0·12 g.) was oxidised with bromine in the usual way, but the resulting lactone would not crystallise. The product, after thorough drying in a vacuum, was dissolved in dry methyl alcohol and the solution saturated with ammonia at 0°. After the mixture had been left for 48 hours at 0° the ammonia and the solvent were removed in a vacuum. The resulting amide slowly crystallised, but could not be recrystallised; it was impure 3-methyl idonamide (Found: N, 4·7. Calc. for $C_7H_{14}O_6N$: N, 6·7%).

Weerman test. The crude 3-methyl idonamide (10 mg.) was dissolved in 2 drops of water, 0·2 c.c. of 1·5N-sodium hypochlorite solution added at 0°, and the mixture kept at 0° for 12 hours. The excess hypochlorite was removed by adding a few crystals of sodium thiosulphate, a little sodium acetate together with a few crystals of semicarbazide hydrochloride were added, and the solution kept overnight at 0°, whereupon 1 mg. of hydrazodicarbonamide (m. p. 258°) separated. A control experiment on gluconamide (10 mg.) carried out in exactly the same way gave 4·5 mg. of hydrazodicarbonamide.

Alkaline Hydrolysis of 4 : 6-*Dimethyl* 2 : 3-*Anhydro-β-methyltaloside.*—The β-methyltaloside (0·385 g.) was dissolved in methyl alcohol (10 c.c.) and heated for 24 hours under reflux with 5% methyl-alcoholic sodium methoxide (10 c.c.). Thereafter the solution was diluted with water and extracted with chloroform. Evaporation of the extract gave a syrup which distilled at 110—120° (bath temp.)/0·03 mm. and showed $n_D^{17°}$ 1·4598, $[\alpha]_D^{17°}$ −70·2° in chloroform (*c*, 1·31) (Found: OMe, 51·8. $C_{10}H_{20}O_6$ requires OMe, 52·5%). This syrup was principally 3 : 4 : 6-*trimethyl β-methyl*-d-*idoside* but probably contained a very small quantity of 2 : 4 : 6-trimethyl β-methylgalactoside. The syrup resisted all attempts to crystallise it.

Conversion of 3 : 4 : 6-*Trimethyl β-Methylidoside into Tetramethyl δ-Idonolactone.*—The syrupy trimethyl β-methyl-*d*-idoside (0·37 g.) was methylated by three treatments with silver oxide and methyl iodide in the usual way to give tetramethyl β-methylidoside, distilling at 95° (bath temp.)/0·03 mm., probably contaminated with a very small amount of tetramethyl β-methylgalactoside. It showed $n_D^{19°}$ 1·4510 and $[\alpha]_D$ −62·8° in chloroform (*c*, 1·625) (Found: OMe, 60·8. Calc. for $C_{11}H_{22}O_6$: OMe, 62·0%). The tetramethyl β-methylidoside was hydrolysed and the product oxidised to the tetramethyl idonolactone by the same procedure as given above for its preparation from 3-methyl β-methylidoside. Crystals were obtained showing m. p. 90° and no depression of m. p. was observed in admixture with authentic tetramethyl δ-idonolactone.

2-*Tosyl* 4 : 6-*Benzylidene α-Methylgalactoside.*—α-Methylgalactoside (25 g.), after being dried in a vacuum at 110°, was shaken with dry acetone (2 l.) containing concentrated sulphuric acid (10 g.) for 4 days. The solution was neutralised with anhydrous sodium carbonate, filtered, and evaporated to dryness in the presence of sodium carbonate. The syrupy product was distilled at 140° (bath temp.)/0·05 mm. (6·5 g.). This could be crystallised, giving 3 : 4-monoacetone α-methylgalactoside (m. p. 103—104°), but this was wasteful and unnecessary. The distilled syrup (6·5 g.) was tritylated by dissolving it in dry pyridine (30 c.c.), adding trityl chloride (8·5 g.), and heating the mixture at 95° for 1 hour. On pouring into water, an amorphous product was obtained (11·5 g.). This substance, 6-trityl 3 : 4-monoacetone α-methylgalactoside, was converted into syrupy 2-tosyl 6-trityl 3 : 4-monoacetone α-methylgalactoside by treatment with tosyl chloride (5·3 g.) in pyridine at 60° for 3 days. After pouring the mixture into water, the product was isolated by extraction with chloroform, and the resulting syrup (11·2 g.) hydrolysed by heating with acetone (300 c.c.) containing 7 c.c. of N-hydrochloric acid under reflux for 5 hours. The solution was neutralised with barium carbonate, filtered, and evaporated to small volume; addition of water precipitated triphenylcarbinol, which was filtered off, and the filtrate evaporated to dryness. After extraction with ethyl acetate a clear syrup, probably 2-tosyl α-methylgalactoside (3·7 g.), was obtained, but again this could not be crystallised. This syrup was treated with benzaldehyde (20 c.c.) and zinc chloride (6 g.) in the usual way and a crystalline compound was isolated. This was 2-*tosyl* 4 : 6-*benzylidene α-methylgalactoside*, m. p. 179—180°, $[\alpha]_D^{18°}$ +117·8° in chloroform (*c*, 0·9) (Found: C, 58·0; H, 5·6; OMe, 7·7. $C_{21}H_{24}O_8S$ requires C, 57·8; H, 5·5; OMe, 7·1%).

2-*Tosyl* 3-*Methyl* 4 : 6-*Benzylidene α-Methylgalactoside.*—The foregoing galactoside (5·8 g.) was methylated with silver oxide and methyl iodide by heating at 45° for 10 hours. After 3 treatments a crystalline *compound* was obtained which, recrystallised from alcohol–chloroform–light petroleum, had m. p. 185°, $[\alpha]_D^{18°}$ +164·4° in chloroform (*c*, 1·435) (Found: C, 58·6; H, 5·9. $C_{22}H_{26}O_8S$ requires C, 58·7; H, 5·8%).

2-*Tosyl α-Methylgalactoside.*—Crystalline 2-tosyl 4 : 6-benzylidene α-methylgalactoside (0·55 g.) was dissolved in acetone (50 c.c.), oxalic acid (2 g.) in water (10 c.c.) added, and the mixture heated under reflux for 12 hours. After neutralisation with barium carbonate, filtration, evaporation of the filtrate, and extraction of the residue with ethyl acetate, syrupy 2-*tosyl α-methylgalactoside* was obtained which, even after this preparation through the crystalline benzylidene compound, could not be crystallised. It showed $[\alpha]_D^{18°}$ +83·5° in methyl alcohol (*c*, 4·54) (Found: OMe, 10·0. $C_{14}H_{20}O_8S$ requires OMe, 8·9%).

2-*Tosyl* 3 : 4 : 6-*Trimethyl α-Methylgalactoside.*—The syrupy 2-tosyl α-methylgalactoside (0·44 g.) was methylated in the usual way by 3 treatments with silver oxide and methyl iodide. The resulting syrup could not be crystallised; yield, 0·4 g., $[\alpha]_D^{18°}$ +74·5° in chloroform (*c*, 3·217) (Found: OMe, 30·7. $C_{17}H_{26}O_8S$ requires OMe, 31·6%).

Action of Alkali on 2-*Tosyl* 4 : 6-*Benzylidene α-Methylgalactoside.*—(a) *Cold sodium methoxide.* The α-methylgalactoside (7·3 g.) was dissolved in chloroform (50 c.c.), a methyl-alcoholic solution containing sodium methoxide (1·1 g.) added, and the mixture set aside for 24 hours. There was, however, no precipitate of sodium *p*-toluenesulphonate. The mixture was diluted with water and extracted with chloroform; evaporation of the extract gave a crystalline solid, which recrystallised from alcohol (m. p. 180°) and was unchanged 2-tosyl 4 : 6-benzylidene α-methylgalactoside (6·8 g.) (mixed m. p.).

(b) *Hot sodium methoxide.* 2-Tosyl 4 : 6-benzylidene α-methylgalactoside (0·9 g.) was dissolved in methyl alcohol (20 c.c.) containing sodium (0·06 g.; 1 atom), and the mixture boiled for 4 hours; thereafter the solution was diluted with water and extracted with chloroform, the extract dried over anhydrous magnesium sulphate, filtered, and evaporated to dryness. After recrystallisation from alcohol the residue gave crystals (m. p. 180°) which were unchanged galactoside (mixed m. p.); yield 0·75 g.

(c) *Hot sodium methoxide under pressure.* 2-Tosyl 4 : 6-benzylidene α-methylgalactoside (0·7 g.) was heated in methyl-alcoholic solution containing sodium (0·06 g.) at 120° in a sealed tube for 20 hours. The product was isolated by dilution with water and extraction with chloroform as before. On evaporation of the chloroform extract, a residue was obtained which was recrystallised from methyl alcohol (m. p. 134°) and was 3-*methyl* 4 : 6-*benzylidene* α-*methyl*-d-*idoside*; yield 0·3 g., $[\alpha]_D^{17°}$ +66·0° in chloroform (*c*, 1·792) (Found: C, 61·1; H, 6·7. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·7%). No other crystalline material could be isolated.

2 : 3-*Dimethyl* 4 : 6-*Benzylidene* α-*Methyl*-d-*idoside*.—3-Methyl 4 : 6-benzylidene α-methylidoside (0·12 g.) was methylated by means of three treatments with silver oxide and methyl iodide at 45°. The resulting product, recrystallised from alcohol, formed long needles (0·12 g.), m. p. 152°, $[\alpha]_D^{15°}$ +68·8° in chloroform (*c*, 1·948) (Found: C, 62·2; H, 7·5; OMe, 29·4. $C_{16}H_{22}O_6$ requires C, 61·9; H, 7·1; OMe, 30·0%).

Action of Methyl-alcoholic Ammonia on 2 : 3-*Anhydro*-β-*methyltaloside*.—2 : 3-Anhydro-β-methyltaloside (0·2 g.) was dissolved in methyl alcohol (50 c.c.), saturated with ammonia gas at 0°, and the solution heated in a sealed tube at 120° for 30 hours. The ammonia and the methyl alcohol were evaporated, and the residue recrystallised from alcohol (0·14 g.); m. p. 192°, $[\alpha]_D^{17°}$ −62·2° in methyl alcohol (*c*, 0·707). It was 3-*amino*-β-*methylidoside* (Found: N, 7·6. $C_7H_{15}O_5N$ requires N, 7·3%). A residual syrup (B, see below) (0·75 g.) was obtained after evaporation of the mother-liquors from the recrystallisation; this, however, could not be crystallised but showed $[\alpha]_D$ −49·9° in ethyl alcohol (*c*, 1·444).

3-*Acetamido Triacetyl* β-*Methyl*-d-*idoside*.—3-Amino-β-methyl-*d*-idoside (30 mg.) was boiled with acetic anhydride (3 c.c.) and fused sodium acetate (0·3 g.) for 2 minutes, the product poured into ice–water, neutralised with sodium bicarbonate, and extracted thoroughly with chloroform. The extract was dried over anhydrous magnesium sulphate, filtered, and evaporated to dryness; the residue, recrystallised from acetone–petrol, (30 mg.) had m. p. 178—179°, $[\alpha]_D^{17°}$ −36·0° in chloroform (*c*, 1·39) (Found: C, 49·4; H, 6·3; N, 4·4. $C_{15}H_{23}O_8N$ requires C, 49·8; H, 6·4; N, 3·9%).

Acetylation of Syrup B.—The syrup B (75 mg.) was acetylated by boiling with acetic anhydride (3 c.c.) and fused sodium acetate (0·3 g.) for 2 minutes. The product was isolated as above, and a syrup was obtained which partly crystallised and from which 3-acetamido triacetyl β-methyl-*d*-idoside (30 mg.) (m. p. 178°) was obtained. A residual syrup (30 mg.) which would not crystallise, remained.

3-*Acetamido*-β-*methyl*-d-*idoside*.—3-Amino-β-methyl-*d*-idoside (45 mg.) was dissolved in dry methyl alcohol (5 c.c.), 3 drops of acetic anhydride added, and the mixture left overnight. Evaporation in a vacuum desiccator over moist potassium hydroxide gave a residue which, recrystallised from alcohol–ether, (35 mg.), had m. p. 202—203°, $[\alpha]_D^{15°}$ −51·4° in methyl alcohol (*c*, 0·935) (Found: C, 45·8; H, 7·3; N, 6·5. $C_9H_{17}O_6N$ requires C, 45·9; H, 7·2; N, 5·9%).

Action of Methyl-alcoholic Ammonia on 4 : 6-*Benzylidene* 2 : 3-*Anhydro*-β-*methyltaloside*.—The anhydro-compound (1 g.) was dissolved in methyl alcohol (150 c.c.), saturated with ammonia at 0°, and the solution heated in a sealed tube at 125° for 50 hrs. The resulting solution was evaporated to dryness, and the product immediately acetylated by dissolving it in pyridine (30 c.c.), adding acetic anhydride (3 c.c.), and keeping it at 35° for 3 days. The mixture was poured into water, extracted with chloroform, the extract washed successively with 5% sulphuric acid, dilute sodium bicarbonate, and with water, dried over anhydrous magnesium sulphate, and evaporated to dryness. The product rapidly crystallised (crude yield, 0·85 g.). This was recrystallised fractionally (0·65 g.), but each crop of crystals melted at 234°. The mother-liquors finally gave a syrup (0·12 g.) which would not crystallise further. The crystalline material was 3-*acetamido* 2-*acetyl* 4 : 6-*benzylidene* β-*methyl*-d-*idoside*, $[\alpha]_D$ −13·1° in chloroform (*c*, 0·848) (Found: C, 59·2; H, 6·3; N, 4·5. $C_{18}H_{23}O_7N$ requires C, 59·2; H, 6·2; N, 3·8%). The syrupy residue probably contained 2-acetamido 3-acetyl 4 : 6-benzylidene β-methylgalactoside.

2-*Tosyl* 3 : 4 : 6-*Trimethyl* β-*Methylgalactoside*.—2-Tosyl β-methylgalactoside (2·3 g.) was treated three times with silver oxide and methyl iodide in the usual way. The product crystallised from ethyl acetate in the form of stout prisms (2·05 g.), m. p. 132°, $[\alpha]_D^{16°}$ −25·1° in chloroform (*c*, 1·356) (Found: C, 52·3; H, 6·8; OMe, 30·7. $C_{17}H_{26}O_8S$ requires C, 52·3; H, 6·7; OMe, 31·7%).

Action of Methyl-alcoholic Ammonia on 2-*Tosyl* 3 : 4 : 6-*Trimethyl* β-*Methylgalactoside*.—The β-methylgalactoside (1·5 g.) was heated at 200° for 40 hrs. with methyl alcohol (200 c.c.), saturated with ammonia at 0°, in a sealed tube. The product was evaporated to dryness, the residue extracted with chloroform, the chloroform solution evaporated, and the syrup distilled at 140°/0·03 mm. as a very mobile liquid (0·3 g.), $n_D^{20°}$ 1·4496. The distillate was acetylated by dissolving it in methyl alcohol (5 c.c.), adding acetic anhydride (2 drops), and keeping it for 24 hrs. After evaporation in a vacuum desiccator over potassium hydroxide, the syrup was distilled at 90—100°/0·02 mm., leaving a crystalline residue which recrystallised from ethyl acetate and a trace of petrol in small needles (m. p. 238°). The yield was only a few mg. and no analytical figures could be obtained, but by analogy with the experiment of Cutler and Peat (J., 1939, 782) the crystalline product should be 2-acetamido 3 : 4 : 6-trimethyl β-methylgalactoside. On admixture with 2-acetyl 3 : 4 : 6-trimethyl β-methylchondrosaminide (m. p. 233°), prepared by Dr. M. Stacey of this department, there was a depression in m. p. to 226—228°, showing that the two compounds were not identical.

A parallel experiment carried out with syrupy 2-tosyl 3 : 4 : 6-trimethyl α-methylgalactoside failed to give any crystalline material.

The author thanks Professor W. N. Haworth, F.R.S., for his help and interest in this investigation.

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[*Received, June 5th*, 1944.]

144. *Triterpene Resinols and Related Acids. Part XVII.* (A) *The Conversion of β-Amyradienonyl Acetate into* allo-β-*Amyrenonyl Acetate.* (B) *The Conversion of β-Amyrin into* iso-β-*Amyradienonol.*

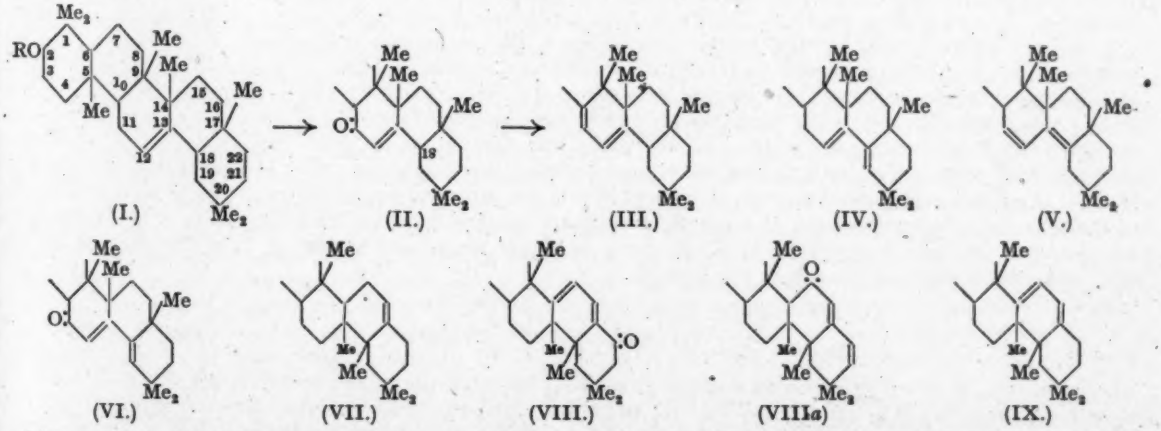
By JAMES GREEN, (the late) NEVILLE MOWER, C. W. PICARD, and F. S. SPRING.

Reduction of β-amyradienonyl acetate (VI, R = Ac) with sodium ethoxide and hydrazine hydrate yields a mixture from which allo-*β-amyrenonyl acetate*, allo-*β-amyrin acetate*, and a mixed crystal containing β-amyradienyl-II acetate have been isolated. *allo*-β-Amyrenonyl acetate is an αβ-unsaturated ketone stereoisomeric with β-amyrenonyl acetate. In terms of the formula (I, R = H) for β-amyrin, *allo*-β-amyrenonyl acetate differs from β-amyrenonyl acetate (II, R = Ac) in the orientation around C_{18}. *allo*-β-Amyrin acetate is probably the corresponding stereoisomer of β-amyrin acetate.

Treatment of *iso*-β-amyrenonyl acetate (XV or XVI, R = Ac) with either selenium dioxide or bromine results in the introduction of a second ethylenic linkage, with the formation of iso-*β-amyradienonyl acetate* (XVII, R = Ac) which is formulated as a de-oxo-derivative of β-amyradiendionyl acetate (XVIII, R = Ac). However, *iso*-β-amyradienonyl acetate cannot be oxidised by means of selenium dioxide to β-amyradiendionyl acetate. The bearing of these results on the elucidation of the structure of the β-amyrin group of triterpenes is discussed.

(A) IN previous Parts of this series it has been shown that reduction of β-amyrenonol (II, R = H) with sodium and ethyl or amyl alcohol yields the addition–reduction compounds, $C_{32}H_{56}O_3$ and $C_{35}H_{62}O_3$, respectively. These compounds are converted into β-amyradienyl-I acetate (III, R = Ac) by treatment with acetic anhydride (Beynon, Sharples, and Spring, J., 1938, 1233; Picard and Spring, J., 1940, 1198). Treatment of the addition reduction complex, $C_{35}H_{62}O_3$, with acetic anhydride also yields the isomeric β-amyradienyl-II acetate, as a minor product (Picard and Spring, J., 1941, 35). β-Amyradienyl-II acetate had previously been obtained by the oxidation of β-amyrin acetate with selenium dioxide (Ruzicka, Müller, and Schellenberg, *Helv. Chim. Acta*, 1939, **22**, 767; Ruzicka and Jeger, *ibid.*, 1941, **24**, 1236). The structure of β-amyradienol-I is securely established as (III, R = H) in terms of the hypothetical formula (I, R = H) for β-amyrin, since it exhibits the light absorption properties of a diene containing a conjugated system in a single six-membered ring, and when oxidised with chromic acid it gives β-amyrenedione (Picard and Spring, 1940, *loc. cit.*). β-Amyradienol-II is either (IV, R = H) or (V, R = H) (cf. Mower, Green, and Spring, J., 1944, 256).

Treatment of β-amyrenonyl acetate (II, R = Ac) with bromine yields β-amyradienonyl acetate which is represented by (VI, R = Ac), again in terms of the formula (I, R = H) for β-amyrin (Picard and Spring, 1941, *loc. cit.*). The hypothetical formula suggested by Bilham, Kon, and Ross (J., 1942, 532, 535, 540) for oleanolic acid leads to the expression (VII, R =H) for β-amyrin. This formulation, which has served the useful purpose of stimulating a more critical examination of the reactions of the β-amyrin group of triterpenes, leads to the expression (VIII, R = Ac) for β-amyradienonyl acetate and related dienones. Kon and Ross (J., 1942, 742) have observed that the alternative structure (VIII*a*) for these dienones is more in harmony with their properties.



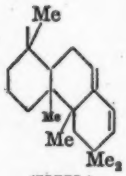
The present communication describes an examination of the reduction of β-amyradienonyl acetate with hydrazine hydrate and sodium ethoxide which was undertaken in order to examine the relationship of this dienone and the two β-amyradienols. A simple replacement of the carbonyl group of β-amyradienonol by methylene would, according to the β-amyrin formula (I, R = H), give the dienol (IV, R = H). A comparison of the product with β-amyradienol-II would allow a decision to be made in favour of one of the alternative formulæ (IV, R = H) and (V, R = H) for β-amyradienol-II. On the other hand, according to the formula (VIII, R = H) for β-amyradienonol, the product should be identical with β-amyradienol-I, which, according to Bilham, Kon, and Ross (*loc. cit.*; p. 538), is represented by (IX, R = H). The reaction product, however, proved to be complex. It was separated by a chromatographic method into three major fractions. The first fraction, obtained by washing the chromatogram with benzene, was acetylated to give allo-*β-amyrin*.

acetate, $C_{32}H_{52}O_2$, m. p. 215—217°, $[\alpha]_D$ +147°. The second fraction from the chromatogram was obtained by continued washing with benzene, and on crystallisation gave an alcohol, $C_{30}H_{48}O$, m. p. 219—220°. This alcohol is very similar in its properties to β-amyradienol-II, m. p. 228—229°, and when mixed with the latter gives an intermediate m. p. The alcohol, m. p. 219—220°, shows the characteristic absorption spectrum of β-amyradienol-II, with maxima at 2430, 2510, and 2600 A., but the intensity of absorption (ε_{2510} = 21,000) is considerably less than that of β-amyradienol-II (ε_{2510} = 31,000). It was not possible appreciably to raise either the m. p. or the intensity of absorption by repeated crystallisation of the alcohol.

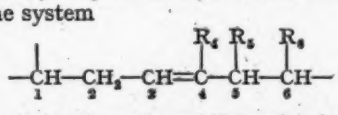
Acetylation of the alcohol, m. p. 219—220°, gave an acetate, m. p. 209—211°, a mixture of which with β-amyradienyl-II acetate (m. p. 228—229°) has m. p. 218—222°. In a second reduction of β-amyrenonyl acetate with hydrazine hydrate and sodium ethoxide, direct crystallisation of the reaction product gave the same alcohol, m. p. 217°, acetylation of which yielded an acetate, m. p. 206—208°, undepressed when mixed with the specimen of m. p. 209—211°; a mixture of this acetate with β-amyradienyl-II acetate shows an intermediate m. p., but a mixture with β-amyradienyl-I acetate shows a marked depression. The acetate, m. p. 206—208°, also exhibits the characteristic triplet absorption spectrum of β-amyradienyl-II acetate with maxima at 2430, 2510, and 2600 A., but the intensity (ε_{2510} = 21,600) was appreciably lower than that observed for the dienyl-II acetate ($\varepsilon_{2510} \approx$ 31,000). The specific rotation of the acetate, m. p. 206—208°, $[\alpha]_D$ +2°, is to be compared with $[\alpha]_D$ +62° for β-amyradienyl-II acetate. The acetate of m. p. 206—208° (and the corresponding alcohol) is almost certainly not homogeneous but a mixed crystal containing β-amyradienyl-II acetate together with a second component. The properties of the acetate, m. p. 206—208°, require that the second component should not exhibit selective absorption of appreciable intensity and that it should have a considerable dextrorotation. It is noteworthy that a 2 : 1 mixture of β-amyradienyl-II acetate and *allo*-β-amyrin acetate would be expected to show the characteristic absorption maxima of the former component with an intensity ε_{2510} = 20,000 and $[\alpha]_D$ +7°, values in fair agreement with those observed for the acetate, m. p. 206—208°.

The final fraction was obtained from the chromatogram by washing with ether. Acetylation of this fraction readily gave allo-β-*amyrenonyl acetate*, $C_{32}H_{50}O_3$, m. p. 262—265°, $[\alpha]_D$ + 67°. It gives a negative unsaturation test with tetranitromethane, and its absorption spectrum shows a well-defined maximum at 2460 A., ε = 11,000; both of these properties indicate that *allo*-β-amyrenonyl acetate is an αβ-unsaturated ketone.

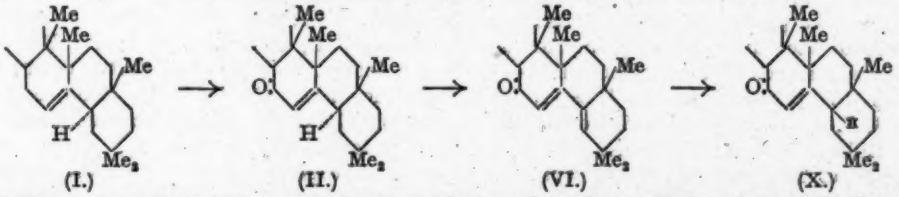
Although evidence for the formation of β-amyradienyl-II acetate from β-amyradienonyl acetate was obtained, but not for that of β-amyradienyl-I acetate, it cannot be claimed that this evidence alone eliminates formula (VIII, R = H) for β-amyradienonol. The complexity of the modified Kishner–Wolff reduction when applied to this conjugated dienone is such that reduction in the sense (VIII) → (XIX) is possible. In the same way it cannot be concluded that the formation of the dienol-II from β-amyradienonyl acetate means that this dienol must be represented by (IV, R = H), since the susceptibility of one of the ethylenic linkages of the dienonol to reduction means that the change (VI) → (V) is not excluded.


(XIX.)

allo-β-Amyrenonyl acetate differs markedly from the isomeric β-amyrenonyl acetate (Picard and Spring, J., 1940, 1200) and from the isomeric *iso*-β-amyrenonyl acetate (Picard, Sharples, and Spring, J., 1939, 1045). Furthermore, there is no reason to suppose that *allo*-β-amyrenonyl acetate differs from β-amyrenonyl acetate in the orientation around C_8, since it has been shown that β-amyrin is unchanged after prolonged heating with sodium ethoxide at 180—190° (Ruzicka and Wirz, *Helv. Chim. Acta*, 1941, **24**, 248). The formation of a new αβ-unsaturated ketone by reduction of β-amyradienonyl acetate is of considerable significance in the structural elucidation of the β-amyrin group of triterpenes. The absolute locations of both the carbonyl and the ethylenic linkage in *allo*-β-amyrenonyl acetate are the same as those in β-amyrenonyl acetate, since the latter is the parent of β-amyradienonyl acetate; the saturation of the terminal ethylenic linkage of β-amyradienonyl acetate has involved the formation of a new asymmetric centre. Our previous experiments in the β-amyrin field (see Picard and Spring, J., 1941, 37) have shown that the unsaturated centre is present in the system

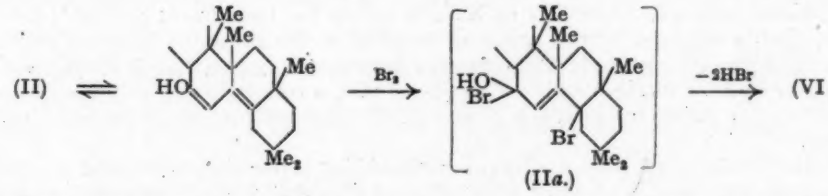


The formation of *allo*-β-amyrenonyl acetate gives the additional information that either C_5 or C_6 (or both) must be asymmetric in β-amyrin, *i.e.*, that R_4 and R_5 cannot both be hydrogens. The hypothetical β-amyrin structure (I) obeys this structural requirement, and represents β-amyrenonyl acetate (II, R = Ac) and *allo*-β-amyrenonyl acetate (X, R = Ac) as isomers differing solely in the orientation around C_{18}: *

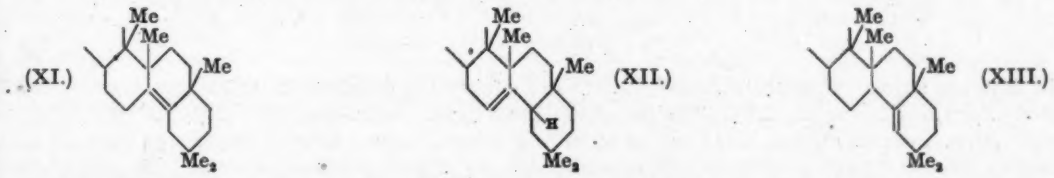

(I.) (II.) (VI.) (X.)

* The steric configurations around C_{18} shown in these formulæ are relative and not absolute.

allo-β-Amyrenonyl acetate is recovered unchanged after treatment with bromine under conditions which convert β-amyrenonyl acetate into β-amyradienonyl acetate (Picard and Spring, 1941, *loc. cit.*). The introduction of a second ethylenic linkage into β-amyrenonyl acetate by means of bromine can be represented as 1:4-addition to the enolic form (II*a*) of β-amyrenonyl acetate followed by loss of hydrogen bromide (see below). The stability of *allo*-β-amyrenonyl acetate is to be attributed to its inability to enolise in the same direction.



The determination of the structure of *allo*-β-amyrin acetate in terms of that of β-amyrin acetate offers more difficulty. Its formation from β-amyradienonyl acetate has involved the replacement of the carbonyl group of the latter by methylene, and the simultaneous reduction of one ethylenic linkage. *allo*-β-Amyrin acetate differs markedly from β-amyrin acetate, and when mixed with this, it gives a large depression in m. p. *allo*-β-Amyrin acetate also differs from the isomeric *epi*-β-amyrin acetate (Ruzicka and Wirz, *Helv. Chim. Acta*, 1941, **24**, 248), which, in its turn, differs from β-amyrin solely in the orientation around C_3. δ-Amyrin acetate (XI, R = Ac) (Ruzicka and Jeger, *Helv. Chim. Acta*, 1941, **24**, 1237; Ruzicka, Jeger, and Norymberski, *ibid.*, 1942, **25**, 457), which is obtained by the catalytic reduction of β-amyradienyl-II acetate (IV or V, R = Ac), is also markedly different from *allo*-β-amyrin acetate. The most probable formulæ for *allo*-β-amyrin acetate are (XII, R = Ac) and (XIII, R = Ac). In (XII, R = Ac) it is represented as derived from *allo*-β-amyrenonyl acetate by simple replacement of the carbonyl by a methylene group, and accordingly differs from β-amyrin acetate solely in the orientation around C_{18}. In (XIII, R = Ac), *allo*-β-amyrin acetate is represented as derived from β-amyradienonyl acetate by the replacement of the carbonyl by methylene and the simultaneous saturation of the Δ^{12}-ethylenic linkage. An attempt to convert *allo*-β-amyrenonyl acetate into *allo*-β-amyrin acetate will be made when the opportunity occurs.

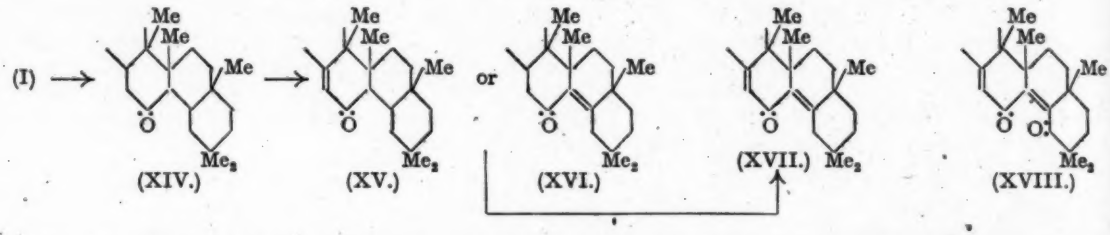


(B) β-Amyradienyl-II acetate is an intermediate in the oxidation of β-amyrin acetate to β-amyradiendionyl acetate, a substance which, together with analogous compounds from the related oleanolic and glycyrrhetic acids, has proved to be of considerable importance in the determination of the nature of the immediate environment of the ethylenic linkage in the β-amyrin group of triterpenes. β-Amyradiendionyl acetate is represented as (XVIII, R = Ac) (Ruzicka and Jeger, *Helv. Chim. Acta*, 1941, **24**, 1236; 1942, **25**, 775, 1409; Ruzicka, Jeger, and Winter, *ibid.*, 1943, **26**, 265; Ruzicka, Jeger, and Ingold, *ibid.*, p. 2278; Kon and Ross, J., 1942, 741; Simpson and Morton, J., 1943, 477). The nature of the chromophore system present in this diendionol has been established by Ruzicka and his collaborators * but there is no direct proof of the exact location of this chromophore in the triterpenoid nucleus. More precisely, it still remains to be established that the carbonyl group of β-amyranonol (J., 1939, 1045) is present in β-amyradiendionol. Our attack on this problem started from the observation that oxidation of β-amyradienyl-I acetate (III, R = Ac) with selenium dioxide gives a mixture of β-amyrenonyl acetate (II, R = Ac) and β-amyradiendionyl acetate (Picard and Spring, J., 1941, 35), which suggested that one of the carbonyl groups of β-amyradiendionyl acetate is either at C_{11} (as in β-amyrenonyl acetate) or at C_{12} (as in *iso*-β-amyrenonyl acetate). An investigation of the action of selenium dioxide on β-amyrenonyl acetate showed that it is oxidised by this reagent to give an acetate,

* Discussing the nature of this compound, Picard and Spring (J., 1941, 35) say that "an examination of its reactions led this author (Simpson, J., 1938, 1313) to the view that it contains an isolated benzenoid ring." Simpson and Morton (J., 1943, 477) comment that "such a view was not expressed in the paper to which they refer and the phrase 'isolated benzenoid ring' or its equivalent does not occur in it." This surprising declamation must be challenged. The substance of the paper by Simpson (*loc. cit.*) is that the compound now known to be β-amyradiendionol contains a benzenoid ring. The burden of positive proof of this conclusion lay in the observation that the compound exhibits an absorption maximum at 2780 A., which is similar in position to (though greater in intensity than) those exhibited by *neo*ergosterol, dihydrotrianhydrostrophanthidin, and dehydro-abietic acid. Each of these compounds contains an *isolated* benzene ring. If a benzene ring conjugated with another unsaturated system was envisaged, the analogies quoted are irrelevant. Again, Simpson and Morton say that Ruzicka, Müller, and Schellenberg (*Helv. Chim. Acta*, 1939, **22**, 767) "have rightly pointed out the inadequacy of an isolated aromatic ring to account for the intensity of absorption." It must, however, be added that Ruzicka and his collaborators also observed that the formal expression used by Simpson (*loc. cit.*) to represent β-amyradiendionol does not allow of conjugation of the postulated benzene ring with any other unsaturated system.

$C_{32}H_{46}O_5$ ("O_5-acetate") in very high yield, and not β-amyradiendionyl acetate (Mower, Green, and Spring, *loc. cit.*). The "O_5-acetate" is also obtained in very high yield by the oxidation of β-amyradienonyl acetate either with selenium dioxide or, as we now find, with chromic anhydride. Once a carbonyl group has been introduced at C_{11}, it is impossible to oxidise the resulting compound to the β-diendionyl acetate, a conclusion in harmony with the postulated formula (XVIII, R = Ac) for the latter. According to the formulation (XVIII), the conjugated system of β-amyradiendionol includes the αβ-unsaturated ketone grouping of *iso*-β-amyrenonol. *iso*-β-Amyrenonyl acetate (XV or XVI, R = Ac) (J., 1939, 1045; J., 1941, 319; Spring, *Ann. Reports*, 1941, **38**, 198) is obtained by the action of bromine on the saturated ketone β-amyranonyl acetate (XIV, R = Ac). The carbonyl group in the saturated ketone, and hence that in *iso*-β-amyrenonyl acetate, is a label marking the position of the double bond of β-amyrin; a conversion of *iso*-β-amyrenonyl acetate into β-amyradiendionyl acetate should be possible if (I) and (XVIII) correctly represent the relationship of β-amyrin and the diendionol.

Picard and Spring (1941, *loc. cit.*) and Ruzicka, Jeger, and Norymberski (*loc. cit.*) have reported unsuccessful attempts to oxidise *iso*-β-amyrenonyl acetate with selenium dioxide. We now find that prolonged treatment of the αβ-unsaturated ketone with selenium dioxide in acetic acid under anhydrous conditions yields iso-β-*amyradienonyl acetate*, $C_{32}H_{48}O_3$, m. p. 208°, which gives a bright yellow coloration with the tetranitromethane reagent whereas the parent *iso*-β-amyrenonyl acetate gives a negative reaction. It exhibits a well-defined absorption maximum at 2450 A., ε = 10,000, and on hydrolysis it is converted into iso-β-*amyradienonol*, $C_{30}H_{46}O_2$, m. p. 239°, which also exhibits the characteristic absorption spectrum with a maximum at 2470 A. and gives a bright yellow colour with the tetranitromethane reagent. *iso*-β-Amyradienonyl acetate is also obtained by treatment of *iso*-β-amyrenonyl acetate with bromine in acetic acid. The most probable structure for *iso*-β-amyradienonyl acetate in terms of that of *iso*-β-amyrenonyl acetate is (XVII, R = Ac).



No data are available for the optical properties of conjugated dienones in which the chromophore is distributed over two rings as in (XVII) but the analogously constituted 3-keto-$\Delta^{11,14}$-cholestadiene (Inhoffen and Huang-Minlon, *Ber.*, 1938, **71**, 1721) and santonin (Ruzicka, Cohen, Furter, and Sluys-Veer, *Helv. Chim. Acta*, 1938, **21**, 1735) each exhibit an absorption maximum at approximately 2400 A. In spite of the close relationship of *iso*-β-amyradienonyl acetate and β-amyradiendionyl acetate according to the hypothetical formulæ (XVII, R = Ac) and (XVIII, R = Ac), *iso*-β-amyradienonyl acetate is recovered unchanged after prolonged treatment with selenium dioxide, under conditions which convert both β-amyrin acetate (I, R = Ac) and δ-amyrin acetate (XI, R = Ac) into the diendionyl acetate. The stability of *iso*-β-amyradienonyl acetate may mean that the diendionyl acetate does not contain a carbonyl group in the same position as that in β-amyranonyl acetate, *i.e.*, that (I, R = H) is an inadequate expression of the structure of β-amyrin. An alternative, but less convincing, conclusion is that oxidation of β-amyrin acetate and its derivatives to β-amyradiendionyl acetate requires in all cases the intermediate formation of β-amyratrienyl acetate (see Newbold and Spring, following paper).

In a further attempt to obtain an intermediate product in the oxidation of β-amyradienyl-II acetate to β-amyradiendionyl acetate, the action of hydrogen peroxide upon the former has been investigated. As minor reaction product an *acetate*, $C_{32}H_{50}O_4$, m. p. 310—313°, was obtained. It is an αβ-unsaturated ketone exhibiting an absorption maximum at 2530 A., ε = 11,000, and it gives a negative test wth the tetranitromethane reagent. The acetate is recovered unchanged after prolonged boiling with acetic anhydride and does not give an oxime under normal reaction conditions. This acetate is not directly related to β-amyradiendionol, since on oxidation with selenium dioxide it gives the "O_5-acetate" identical with that prepared by similar oxidation of β-amyrenonyl acetate. The major product of the oxidation of β-amyradienyl-II acetate with hydrogen peroxide proved to be of little interest in the present study. It is a *diacetate*, $C_{34}H_{50}O_6$ or $C_{34}H_{48}O_6$, m. p. 238°, which gave a negative tetranitromethane test and showed no selective absorption of appreciable intensity above 2200 A.

Experimental.

Reduction of β-Amyradienonyl Acetate.—(*a*) The dienonyl acetate {Picard and Spring, J., 1941, 35; m. p. 248—249°; $[\alpha]_D^{15°}$ +342° (*l* = 1, *c* = 1·1 in pyridine), 1·3 g.} was heated in a sealed tube at 200° for 12 hours with a solution of sodium ethoxide in alcohol (1·2 g. of sodium in 30 c.c. of alcohol) and hydrazine hydrate (99·5%; 3·4 c.c.). The cold solution was poured into water, and the neutral product isolated by means of ether. The ethereal solution was washed with hydrochloric acid, then with water, and dried (sodium sulphate). The residue (1·0 g.) obtained after removal of the ether was dried in a vacuum at 100°, dissolved in a mixture of light petroleum (b. p. 40—60°) (50 c.c.) and benzene (20 c.c.), and filtered through a column (21 × 3 cm.) of activated alumina (Brockmann). The column was washed

successively with light petroleum (b. p. 40—60°), light petroleum–benzene, benzene, and ether to give the following fractions :

	Solvent, c.c.	Wt. of fraction, g.		Solvent, c.c.	Wt. of fraction, g.
1	Light petroleum, 300	nil	6	Benzene 250	0·3
2	,, ,, 250	,,	7	,, ,, ...	0·2
3	Light petroleum–benzene (1 : 1), 250	,,	8	,, ,, ...	0·02
4	,, ,, ,, ,,	trace	9	Ether, 250	0·32
5	Benzene, 250	0·05	10	,, ,, ...	nil

Fraction 6 was difficult to crystallise. It separated in a crystalline condition on careful cooling of a solution in methanol, but it showed a great tendency to separate in a gelatinous form. The fraction was reconstituted by removal of solvent, dried, and acetylated by heating on the steam-bath for 1 hour with pyridine (6 c.c.) and acetic anhydride (4 c.c.). The product was crystallised thrice from methanol–acetone, from which allo-*β-amyrin acetate* separated in plates, m. p. 215—217°, $[\alpha]_D^{20°}$ +147° (*l* = 0·5, *c* = 1·3 in pyridine); it gives a pale yellow colour with tetranitromethane in chloroform. When mixed with *β*-amyradienyl-II acetate the m. p. was depressed to 203—207° (Found : C, 81·9; H, 10·9. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2%).

Fraction 7 separated from aqueous alcohol as plates, m. p. 216—217·5°. After two further crystallisations from acetone, this alcohol was obtained as plates, m. p. 219—220°. It gives a brown coloration with tetranitromethane in chloroform. When mixed with *β*-amyradienol-II it melted at 220·5—221° (Found : C, 85·2; H, 11·4. Calc. for $C_{30}H_{48}O$: C, 84·8; H, 11·4. Calc. for $C_{30}H_{50}O$: C, 84·4; H, 11·8%). *Light absorption in alcohol :* Principal maximum at 2510 A., ε = 21,000, with subsidiary maxima at 2430 and 2600 A. Ruzicka, Müller, and Schellenberg (*loc. cit.*) give max. 2510, log ε = 4·5 for *β*-amyradienol-II. The alcohol (20 mg.) was acetylated by heating on the steam-bath with pyridine (1 c.c.) and acetic anhydride (1 c.c.) for 30 minutes. The product was precipitated by addition of water, filtered, dried, and crystallised twice from methanol–acetone, from which the acetate separated as plates, m. p. 209—211°.

Fraction 9 from the chromatogram separated from aqueous alcohol as prismatic needles. As the purification of the free alcohol was wasteful, the fractions were combined, the solvents removed, and the residue was acetylated by 14 hours' keeping with pyridine (1 c.c.) and acetic anhydride (1 c.c.). The mixture was then heated on the steam-bath for 10 minutes, and the acetate isolated in the usual way by means of ether. After three crystalllisations from methanol–acetone, allo-*β-amyrenonyl acetate* separated as iridescent plates, m. p. 262—265°—depressed to 248·5—250° when mixed with *β*-amyrenonyl acetate (m. p. 260—261°); $[\alpha]_D^{18°}$ +67° (*l* = 0·5, *c* = 0·5 in chloroform) (Found : C, 79·8; H, 10·6. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·45%). *Light absorption in alcohol :* Maximum at 2460 A., ε = 11,000.

(*b*) *β*-Amyradienonyl acetate (0·7 g.) was heated in an autoclave for 12 hours at 200° with an alcoholic solution of sodium ethoxide (0·6 g. of sodium in 12 c.c. of alcohol) and hydrazine hydrate (90%; 1·7 c.c.). The cold reaction mixture was poured into water, and the neutral product isolated by means of ether. The product was crystallised from acetone containing a small amount of methyl alcohol, giving needles, m. p. 208—211°, which after two further crystallisations from acetone had m. p. 217° (100 mg.); the m. p. could not be raised appreciably by repeated crystallisation. This alcohol gives an intense red-brown colour with tetranitromethane in chloroform, and when mixed with *β*-amyradienol-I (m. p. 215·5—216·5°) the m. p. was depressed to 175—180°. When mixed with *β*-amyradienol-II (m. p. 228·5°), the m. p. was 218·5—220°. The alcohol, m. p. 217°, was acetylated in the usual manner, and the product crystallised from alcohol to give needles, m. p. 199·5—200·5°, which after two recrystallisations from aqueous acetone formed plates, m. p. 201—202°; $[\alpha]_D^{23°}$ +2° (*l* = 1, *c* = 2 in chloroform); mixed with *β*-amyradienyl-II acetate (m. p. 226°) the m. p. was 210—212°. A solution of the acetate, m. p. 201—202° (25 mg.), in light petroleum (b. p. 40—60°; 35 c.c.) was filtered through a column of activated alumina (10 × 1·5 cm.) and the column washed to give the following fractions :

	Solvent, c.c.	Wt. of fraction.		Solvent, c.c.	Wt. of fraction.
1	Light petroleum (b. p. 40—60°), 110	traces	3	Benzene, 125	20 mg.
2	,, ,, ,, ,, 120	nil	4	,, ,, ...	nil

Fraction 3 separated from acetone as plates, m. p. 206—208°, $[\alpha]_D$ +2° (*l* = 0·5, *c* = 2·0 in chloroform); when mixed with the acetate of m. p. 209—211°, the m. p. was 208—209°. *Light absorption in alcohol :* Maxima at 2430, 2510, and 2600 A., ε_{2510} = 22,000.

Oxidation of β-Amyradienyl-II Acetate with Hydrogen Peroxide.—A solution of this acetate (4 g.) in glacial acetic acid (200 c.c.) was treated during 20 minutes with hydrogen peroxide (100-vol.; 10 c.c.) with stirring on the steam-bath. The mixture was heated for a further 2 hours on the steam-bath, and the cold solution precipitated with water. The solid was collected, dried, and fractionally crystallised from acetone. The least soluble crop (fraction A) separated as needles which melted at 283° after sintering at 224°. After three more crystallisations from acetone, the *compound*, $C_{32}H_{50}O_4$, was obtained as small prisms, m. p. 310—313° (sintering at 304°). By concentration of the mother-liquors obtained during the crystallisation of fraction A, further small crops of the same compound were obtained (total yield, *ca.* 35 mg.). It gives a negative reaction with the tetranitromethane reagent (Found : C, 76·6; H, 9·9. $C_{32}H_{50}O_4$ requires C, 77·0; H, 10·1%). *Light absorption in alcohol :* Maximum at 2533 A., ε = 11,000.

Although various changes were made in the reaction conditions in three different experiments, the yield of the compound $C_{32}H_{50}O_4$ could not be appreciably increased.

Concentration of the original acetone mother-liquor from fraction A gave a more soluble product which, after repeated crystallisation from methanol, gave the major oxidation product as fine needles, m. p. 238°, evidently a *diacetate* (Found : C, 73·4; H, 8·6. Ac, 15·5. $C_{34}H_{50}O_6$ requires C, 73·6; H, 9·1. 2Ac, 15·5. $C_{34}H_{48}O_6$ requires C, 73·9; H, 8·7. 2Ac, 15·6%). With tetranitromethane in chloroform, it gives only a very pale yellow coloration, and it does not give a coloration with aqueous ferric chloride solution. It is recovered unchanged after being heated with acetic anhydride, and does not contain any active hydrogen (Zerewitinoff).

" O_3-Acetate " from Compound $C_{32}H_{50}O_4$.—This compound (33 mg.) in glacial acetic acid (2 c.c.) was refluxed with selenium dioxide (70 mg.) for 6 hours. The solution was filtered from selenium, the filtrate precipitated with water, and the solid collected and dried. Two crystallisations from methyl alcohol gave the " O_3-acetate " as fine white needles, m. p. 251·5—252° undepressed when mixed with a specimen prepared by oxidation of *β*-amyrenonyl acetate with selenium dioxide (Mower, Green, and Spring, *loc. cit.*). *Light absorption in alcohol :* Maximum at 2260 A., ε = 3,600.

iso-*β-Amyradienonyl Acetate.*—(*a*) *iso*-*β*-Amyrenonyl acetate (m. p. 288°; 2·0 g.) in boiling glacial acetic acid (60 c.c.) was refluxed for 20 hours with powdered selenium dioxide (2·0 g.). The hot mixture was filtered from selenium, and the yellow-green filtrate treated with water. The solid was collected, washed with water, and dried in an air-oven (1·9 g.). Crystallisation of this solid from aqueous acetone yielded well-defined plates (1·2 g.), m. p. 204°, which after a second crystallisation from the same solvent had m. p. 206° (0·8 g.) and gave a bright yellow colour with the tetra-

nitromethane reagent. A solution of this solid (770 mg.) in benzene (30 c.c.) was filtered through a column of activated alumina (20 g.), and the column washed with benzene. After removal of the benzene, the residue was twice crystallised from aqueous acetone, giving iso-*β-amyradienonyl acetate* (0·4 g.) as plates, m. p. 208°; $[\alpha]_D^{18°}$ — 36·5° (l = 1, c = 0·7 in chloroform). It gives an intense yellow colour with tetranitromethane in chloroform (Found: C, 80·0; H, 10·1. $C_{32}H_{48}O_3$ requires C, 80·0; H, 10·1%).

iso-*β-Amyradienonol* was obtained by refluxing the acetate (200 mg.) for 3 hours with methanolic potassium hydroxide (5%; 20 c.c.). The product, isolated by means of ether, separated from methyl alcohol as hard prisms, m. p. 239° (Found: C, 81·9; H, 10·5. $C_{30}H_{46}O_2$ requires C, 82·1; H, 10·6%).

(*b*) A solution of *iso-β*-amyrenonyl acetate (600 mg.) in glacial acetic acid (25 c.c.) was treated at 75—80° with a solution of bromine in glacial acetic acid (3%; 7·5 c.c.) added dropwise over 15 minutes. Hydrogen bromide was evolved. The pale yellow solution was kept at 80° for another hour, and the product collected by addition of water and filtration. The pale yellow solid was dried in a desiccator, and fractionally crystallised from methanol. The first crop (270 mg., plates) after three recrystallisations from methylated spirit gave *iso-β*-amyrenonyl acetate as plates, m. p. 282—283° undepressed when mixed with a specimen of the starting material. The second crop (30 mg.; m. p. 267—273°) proved to be impure *iso-β*-amyrenonyl acetate. The third crop (100 mg.), obtained by further concentration of the methanolic mother-liquor from the second crop, separated as plates, m. p. 200—203°, which after two recrystallisations from aqueous acetone gave *iso-β*-amyradienonyl acetate as plates, m. p. 204—206° undepressed when mixed with the specimen prepared by method (*a*). It gives a bright yellow colour with the tetranitromethane reagent.

THE UNIVERSITY, MANCHESTER. [*Received, July 13th*, 1944.]

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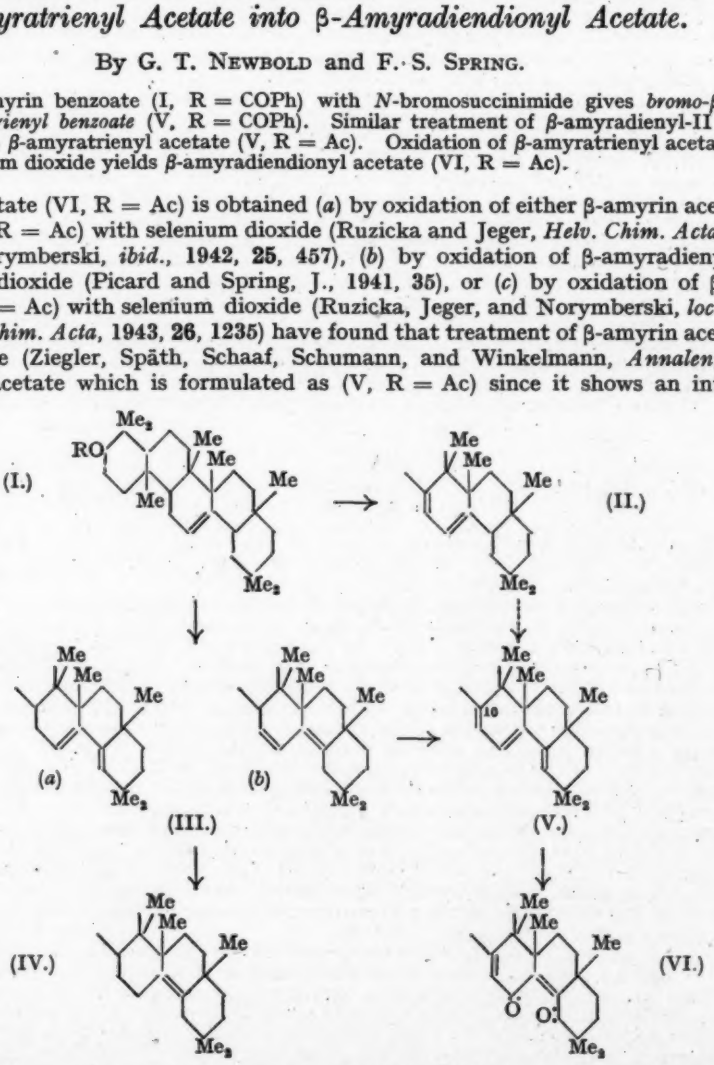
145. *Triterpene Resinols and Related Acids. Part XVIII. The Conversion of β-Amyratrienyl Acetate into β-Amyradiendionyl Acetate.*

By G. T. NEWBOLD and F. S. SPRING.

Treatment of β-amyrin benzoate (I, R = COPh) with *N*-bromosuccinimide gives *bromo-β-amyratrienyl benzoate* and *β-amyratrienyl benzoate* (V, R = COPh). Similar treatment of β-amyradienyl-II acetate (III*a* or III*b*, R = Ac) gives β-amyratrienyl acetate (V, R = Ac). Oxidation of β-amyratrienyl acetate with either chromic acid or selenium dioxide yields β-amyradiendionyl acetate (VI, R = Ac).

β-AMYRADIENDIONYL acetate (VI, R = Ac) is obtained (*a*) by oxidation of either β-amyrin acetate (I, R = Ac) or δ-amyrin acetate (IV, R = Ac) with selenium dioxide (Ruzicka and Jeger, *Helv. Chim. Acta*, **1941**, **24**, 1236; Ruzicka, Jeger, and Norymberski, *ibid.*, **1942**, **25**, 457), (*b*) by oxidation of β-amyradienyl-I acetate (II, R = Ac) with selenium dioxide (Picard and Spring, J., **1941**, 35), or (*c*) by oxidation of β-amyradienyl-II acetate (III*a* or III*b*, R = Ac) with selenium dioxide (Ruzicka, Jeger, and Norymberski, *loc. cit.*). Ruzicka, Jeger, and Redel (*Helv. Chim. Acta*, **1943**, **26**, 1235) have found that treatment of β-amyrin acetate (I, R = Ac) with *N*-bromosuccinimide (Ziegler, Späth, Schaaf, Schumann, and Winkelmann, *Annalen*, **1942**, **551**, 80) gives a β-amyratrienyl acetate which is formulated as (V, R = Ac) since it shows an intense absorption



maximum at 3080 A. The appearance of this paper makes it desirable to record certain experiments which establish another link in the chain of reactions involved in the conversion of β-amyrin (I, R = H) into β-amyradiendionol (VI, R = H).

Treatment of β-amyrin benzoate (I, R = COPh) with *N*-bromosuccinimide in carbon tetrachloride gives a mixture from which was isolated *bromo-β-amyratrienyl benzoate*, m. p. 211—212°, $[\alpha]_D$ + 673°, which shows an intense absorption maximum at 3160 A. Hydrolysis of this benzoate gave *bromo-β-amyratrienol*, m. p. 160—170°, which also exhibits an absorption maximum at 3160 A. Concentration of the original mother-liquors of bromo-β-amyratrienyl benzoate gave *β-amyratrienyl benzoate* (V, R = COPh), m. p. 202—204°, $[\alpha]_D$ + 536°, hydrolysis of which yielded β-amyratrienol (V, R = H) identical with that described by Ruzicka, Jeger, and Redel (*loc. cit.*).

Treatment of β-amyradienyl-II acetate (III*a* or III*b*, R = Ac) with *N*-bromosuccinimide gave β-amyratrienyl acetate (V, R = Ac), whereas reaction of the bromo-imide with β-amyradienyl-I acetate (II, R = Ac) did not proceed smoothly: the product, m. p. 170—178°, which was not obtained pure, showed no depression of m. p. when mixed with a specimen of β-amyratrienyl acetate and had the characteristic absorption spectrum of the latter (max. 3080 A., ε = 9000).

According to the provisional formula (I, R = H) for β-amyrin, the conjugated system in β-amyratrienyl acetate (V, R = Ac) is spread over the same part of the triterpenoid nucleus as that in β-amyradiendionyl acetate (VI, R = Ac). That these relative formulations are correct was established by an examination of the oxidation of the trienyl acetate. Oxidation of β-amyratrienyl acetate with chromic acid gives β-amyradiendionyl acetate. Again, with acetic acid as solvent, β-amyratrienyl acetate is smoothly oxidised by selenium dioxide to give β-amyradiendionyl acetate. The conditions employed for the chromic acid oxidation of the trienyl acetate did not give the oxide of β-amyradiendionyl acetate (Ruzicka and Jeger, *Helv. Chim. Acta*, 1942, **25**, 1409), which is known to result from the further chromic acid oxidation of β-amyradiendionyl acetate (Simpson, J., 1938, 1313). It is noteworthy that, had the oxidation of β-amyratrienyl acetate primarily involved the Δ^{10}-linkage, β-amyradienonyl acetate (Picard and Spring, *loc. cit.*) would be expected as an intermediate, and it is known that oxidation of β-amyradienonyl acetate with chromic acid gives the acetate $C_{32}H_{46}O_5$ ("O_5-acetate") and not β-amyradiendionyl acetate (Green, Mower, Picard, and Spring, preceding paper). Neither β-amyradienonyl acetate nor the "O_5-acetate" was detected as a product of the oxidation of β-amyratrienyl acetate.

Experimental.

Bromo-β-amyratrienyl Benzoate.—β-Amyrin benzoate (5 g.) in carbon tetrachloride (200 c.c.) was refluxed with *N*-bromosuccinimide (96%; 5 g.) for 3 hours. Hydrogen bromide was evolved throughout, and the solution gradually became red. The cold solution was filtered, and the filtrate washed successively with dilute sodium hydroxide solution, hydrochloric acid, and water. Removal of the solvent from the dried solution gave a resin which crystallised from acetone. Seven recrystallisations from the same solvent gave *bromo-β-amyratrienyl benzoate* as heavy plates, m. p. 211—212° (0·5 g.). It gives a deep brown coloration with tetranitromethane in chloroform, and a strong positive Beilstein test; $[\alpha]_D^{18°}$ + 673° (l = 1, c = 2·2 in chloroform) (Found: C, 73·7; H, 8·2. $C_{37}H_{49}O_2Br$ requires C, 73·4; H, 8·2%). *Light absorption in alcohol:* Maximum at 3160 A., ε = 11,300.

Hydrolysis of the benzoate with 10% alcoholic potassium hydroxide gave *bromo-β-amyratrienol*, m. p. 160—170°, separating as plates from aqueous alcohol, and giving a strong positive Beilstein test (Found: C, 71·5; H, 9·0. $C_{30}H_{45}OBr$ requires C, 71·8; H, 9·0%). *Light absorption in alcohol:* Maximum at 3160 A., ε = 10,400.

β-Amyratrienyl Benzoate.—The mother-liquors remaining after the isolation of bromo-β-amyratrienyl benzoate were combined and evaporated, and the residue dissolved in methanol. A crop of ill-defined needles, m. p. 161—166°, separated which on recrystallisation from methanol gave a top crop, m. p. 182—188°, containing halogen; when mixed with bromo-β-amyratrienyl benzoate this gave an intermediate m. p. The second crop formed needles, m. p. 185—193°, raised by recrystallisation from acetone to 193—199°; when mixed with bromo-β-amyratrienyl benzoate, the m. p. was depressed to 170—182°. After four crystallisations from aqueous acetone, this gave *β-amyratrienyl benzoate*, m. p. 202—204°, $[\alpha]_D^{16·5°}$ + 536° (l = 1, c = 0·3 in chloroform) (yield, 100 mg.), as fine needles which gave a negative Beilstein test (Found: C, 84·05; H, 9·3. $C_{37}H_{50}O_2$ requires C, 84·35; H, 9·6%). Hydrolysis of β-amyratrienyl benzoate with alcoholic potassium hydroxide (10%) gave β-amyratrienol as fine needles from aqueous acetone, m. p. 185—187° undepressed when mixed with a specimen of the trienol (m. p. 183—184°) prepared by hydrolysis of β-amyratrienyl acetate (Ruzicka, Jeger, and Redel, *loc. cit.*); $[\alpha]_D^{18°}$ + 563° (l = 1, c = 0·36 in chloroform). *Light absorption in alcohol:* Maximum at 3120 A., ε = 12,000.

β-Amyratrienyl Acetate from β-Amyradienyl-II Acetate.—The dienyl-II acetate (1 g.) in absolute carbon tetrachloride (50 c.c.) was heated under reflux for 3 hours with *N*-bromosuccinimide (0·6 g.; 99%). Hydrogen bromide was evolved. The product, isolated in the usual manner, was crystallised five times from acetone to give β-amyratrienyl acetate as blades, m. p. 184—185°, showing no depression with an authentic specimen; $[\alpha]_D^{18°}$ + 560° (l = 1, c = 0·61 in chloroform).

Treatment of β-Amyradienyl-I Acetate with N-Bromosuccinimide.—The dienyl-I acetate (0·2 g.) in carbon tetrachloride (15 c.c.) was refluxed with *N*-bromosuccinimide (0·2 g.; 80%) for 2 hours. The mixture was filtered, and the filtrate washed successively with dilute sodium hydroxide solution, dilute acid, and water. The solvent was removed from the dried solution, and the residue heated on the water-bath in a high vacuum. A solution of the resinous residue in light petroleum (b. p. 40—60°)–benzene (1 : 1; 50 c.c.) was filtered through a column of activated alumina (Brockmann, 25 g.), and the column washed with the same solvent mixture to give the following fractions:

	Vol. of solvent, c.c.	Wt. of fraction, mg.	M. p.
1	50	50	160—172°
2	100	55	161—172
3	200	20	(Oil)

Fractions 1 and 2, which showed no depression in m. p. when mixed, were combined and crystallised twice from aqueous acetone, from which the impure β-amyratrienyl acetate separated as blades, m. p. 170—178°; mixed m. p. with β-amyratrienyl acetate, 175—181°. The acetate, m. p. 170—178°, gave a negative Beilstein test for halogen. *Light absorption in alcohol:* Maximum at 3080 A., ε = 9000.

β-Amyradiendionyl Acetate.—(*a*) β-Amyratrienyl acetate (0·5 g.) in glacial acetic acid (30 c.c.) was heated under reflux with selenium dioxide (0·5 g.) for 16 hours. The hot solution was filtered from red selenium, and the filtrate

evaporated under reduced pressure. After the addition of water, the product was extracted with ether, the extract washed with water, dried (sodium sulphate), and the solvent removed. After four crystallisations of the residue from aqueous methanol, β-amyradiendionyl acetate (150 mg.) was obtained as colourless plates, m. p. 235—237°, undepressed when mixed with a specimen prepared from β-amyrin acetate. It gave a negative reaction with the tetranitromethane reagent (Found: C, 77·4; H, 9·45. Calc. for $C_{32}H_{46}O_4$: C, 77·7; H, 9·4%). *Light absorption in alcohol:* Maximum at 2785 A., ε = 11,800.

(*b*) β-Amyratrienyl acetate (0·4 g.) in boiling stabilised glacial acetic acid (35 c.c.) was treated with a solution of chromic anhydride (320 mg.) in water (0·5 c.c.) and acetic acid (15 c.c.) added over ½ hour. The solution was refluxed for a further hour. After the addition of a little methanol, the solvent was removed under reduced pressure, and the residue shaken with ether and dilute sulphuric acid. The ethereal extract was washed with dilute sodium hydroxide solution, then with water, and dried (sodium sulphate). Removal of the ether and crystallisation of the residue from aqueous methanol (seven times) gave β-amyradiendionyl acetate (100 mg.) as heavy plates, m. p. 235—237°, either alone or mixed with an authentic specimen; it gives a negative reaction with the tetranitromethane reagent (Found: C, 77·4; H, 9·4%). *Light absorption in alcohol:* Maximum at 2790 A., ε = 12,000.

THE UNIVERSITY, MANCHESTER. [*Received, July 13th*, 1944.]

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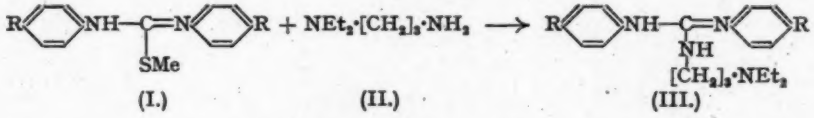
146. *Some Derivatives of Diphenylguanidine.*

By M. J. S. DEWAR.

Certain diaryl-(γ-diethylaminopropyl)guanidines have been synthesised with a view to pharmacological tests.

SEVERAL lines of investigation suggested that diphenylguanidine derivatives containing a second basic centre in the molecule might have interesting pharmacological properties; three such compounds have therefore been synthesised by condensing an appropriate diphenylmethyl*iso*thiourea derivative (I) with γ-diethylaminopropylamine (II) to form a guanidine derivative (III) by loss of methylthiol. The necessary *iso*thioureas were prepared by the method of Deck and Dains (*J. Amer. Chem. Soc.*, 1933, **55**, 4986) from the corresponding thiourea and methyl sulphate. *4 : 4′-Dichloro-* (I; R = Cl) and *4 : 4′-dimethoxy-diphenylisothioureas* (I; R = OMe) have not previously been described. Condensation with (II) proceeded smoothly to give excellent yields of the guanidine (III; R = H, Cl or OMe), but only their *oxalates* could be obtained crystalline, except that diphenyl-(γ-diethylaminopropyl)guanidine (III; R = H) gave also a crystalline *picrolonate*. For pharmacological test the *hydrochlorides* were prepared; they were intractable gums which, however, gave satisfactory analyses.



(I.) (II.) (III.)

EXPERIMENTAL.

(All compounds were dried in a high vacuum at 60° for analysis.)

N′N″-Diphenyl-N-(γ-diethylaminopropyl)guanidine.—Diphenylmethyl*iso*thiourea (9·68 g.) (Deck and Dains, *loc. cit.*) and γ-diethylaminopropylamine (5·20 g.) were dissolved in xylene (30 c.c.) and boiled for 15 hours under reflux. The guanidine *oxalate*, precipitated in theoretical yield by addition of excess oxalic acid in ethyl acetate, crystallised from alcohol in colourless felted needles, m. p. 99° (Found: C, 55·1; H, 6·5; N, 10·9. $C_{20}H_{28}N_4,2C_2H_2O_4,H_2O$ requires C, 55·2; H, 6·5; N, 10·7%). The *picrolonate* crystallised from acetone after a month and was recrystallised with seeding from alcohol, forming orange rhombs, m. p. 111° with gas-evolution (Found: C, 55·2; H, 5·4; N, 19·1. $C_{20}H_{28}N_4,2C_{10}H_8O_5N_4,H_2O$ requires C, 55·2; H, 5·3; N, 19·3%). Other derivatives could not be obtained crystalline.

Dianisylmethylisothiourea.—Prepared in 88% yield by the method of Deck and Dains (*loc. cit.*), the *iso*thiourea crystallised from benzene–light petroleum in large polyhedra, m. p. 84—85° (Found: C, 63·1; H, 5·8; S, 10·1. $C_{16}H_{18}O_2N_2S$ requires C, 63·5; H, 6·0; S, 10·6%).

Bis-(p-chlorophenyl)methylisothiourea.—Prepared similarly in 89% yield, the *iso*thiourea crystallised from ether–light petroleum in colourless needles, m. p. 133° (Found: C, 53·8; H, 3·9. $C_{14}H_{12}N_2Cl_2S$ requires C, 54·0; H, 3·9%).

N′N″-Dianisyl-N-(γ-diethylaminopropyl)guanidine.—Prepared in the same way as the diphenylguanidine and in almost theoretical yield, this guanidine gave an *oxalate* which crystallised only with extreme difficulty and showed dimorphism; rounded rhombs, m. p. 100—105°, separated first from alcohol, and these gradually changed into pale yellow prisms, m. p. 150° with gas-evolution (Found: C, 50·6; H, 7·0; N, 9·3. $C_{22}H_{32}O_9N_4,2C_2H_2O_4,3H_2O$ requires C, 50·5; H, 6·8; N, 9·1%). No other derivative could be obtained crystalline; the *hydrochloride* was an extremely hygroscopic gum (Found: C, 56·9; H, 8·0; N, 12·2. $C_{22}H_{32}O_2N_4,2HCl,\frac{1}{2}H_2O$ requires C, 56·7; H, 7·5; N, 12·0%).

N′N″-Bis-(p-chlorophenyl)-N-(γ-diethylaminopropyl)guanidine.—Prepared similarly, the guanidine *oxalate* crystallised with great reluctance from alcohol in feathery, cream-coloured needles, m. p. 166—168° with gas-evolution (Found: C, 49·4; H, 5·7; N, 9·4. $C_{20}H_{26}N_4Cl_2,2C_2H_2O_4,\frac{1}{2}H_2O$ requires C, 49·5; H, 5·3; N, 9·6%). No other derivative could be obtained crystalline; the *hydrochloride* was an exceptionally hygroscopic gum (Found: C, 50·9; H, 6·6; N, 11·7. $C_{20}H_{26}N_4Cl_2,2HCl,\frac{1}{2}H_2O$ requires C, 51·0; H, 6·1; N, 11·9%).

The author thanks Professor Sir Robert Robinson, F.R.S., for his advice and encouragement in this work, and also Imperial Chemical Industries Limited, Dyestuffs Division, for facilities.

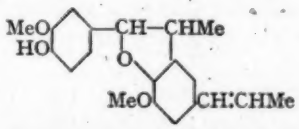
DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, August 5th*, 1944.]

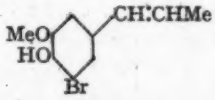
147. *The Constituents of Natural Phenolic Resins. Part XIX. The Oxidation of Ferulic Acid.*

By Neville J. Cartwright and Robert D. Haworth.

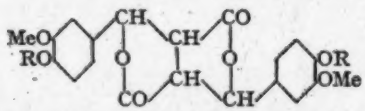
It has previously been suggested that the lignans are derived by oxidative coupling of *n*-propenylphenol derivatives at the β-carbon atom of the side chain. This type of oxidative coupling has now been experimentally realised by the conversion of ferulic acid into " dehydrodiferulic acid " (20% yields) by the action of either ferric chloride or ammonium persulphate. Constitution (III; R = H) assigned to the oxidation product has been established by hydrolysis of the dimethyl ether to veratraldehyde and veratrylidenesuccinic acid, and also by cyclisation and dehydrogenation to the anhydride of 6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)-naphthalene-2 : 3-dicarboxylic acid.

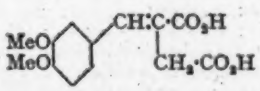
The oxidation of phenols to peroxides (Pummerer, *Ber.*, 1914, **47**, 1472; Goldschmidt and Schmidt, *ibid.*, 1922, **55**, 3197), diphenyl ethers (Pummerer, *ibid.*, 1925, **58**, 1808; Erdtman, *Svensk. Kem. Tids.*, 1934, **46**, 226), 2 : 2′- or 4 : 4′-dihydroxydiphenyls (Dianin, *Ber.*, 1873, **6**, 1252; Tiemann, *ibid.*, 1885, **18**, 3493; Cousin and Heressey, *Bull. Soc. chim.*, 1908, **3**, 1066, 1070) involves coupling at the anionoid centres of the molecules. The β-carbon atom of the side chain of a *p*-hydroxypropenylbenzene may acquire this character in virtue of the extended conjugation and analogous coupling may be expected. The oxidation of *iso*eugenol to dehydro*iso*-eugenol (I) (Erdtman, *Annalen*, 1933, **503**, 283) involves a union between the anionoid centre of the side chain and the *o*-position with respect to the phenolic group in a second molecule. The suggestion (J., 1942, 455) that natural lignans are derived from two *p*-hydroxypropenylbenzene molecules by oxidation at the β-carbon atom in the side chain arose from a further application of these views, but no examples of such coupling have been reported previously.

(I.) 

 (II.)

5-Bromo*iso*eugenol (II), in which the reactive nuclear positions were not available, appeared to be a favourable case for the realisation of side-chain union. 5-Bromovanillin (Tiemann and Haarmann, *Ber.*, 1874, **7**, 615) was converted by treatment with ethylmagnesium iodide into *α-(5-bromo-4-hydroxy-3-methoxyphenyl)-propyl alcohol*, but dehydration of this to 5-bromo*iso*eugenol (II) presented difficulties. In a few experiments the dehydration was successfully accomplished by the action of excess of ethylmagnesium iodide, but the yields were very variable, and excessive polymerisation occurred when alternative dehydrating agents were selected. It was then discovered that ferulic acid (4-hydroxy-3-methoxycinnamic acid) was oxidised by ferric chloride in aqueous-alcoholic solution. A brown ferric salt gradually separated, which was decomposed by acids to a crystalline substance, $C_{20}H_{18}O_8$, m. p. 211° (decomp.). After the completion of our experiments it was found that Erdtman (*Svensk. Kem. Tids.*, 1935, **47**, 223) had previously obtained 9% yields of the same compound, " dehydrodiferulic acid," by a similar method, but apart from suggesting that the compound was an alkali-unstable phenolic lactone of the above composition, he was unable to elucidate the structure with the material at his disposal. We have shown that this compound may be obtained in 20% yield by oxidising ferulic acid with ammonium persulphate, and also in 22% yield with ferric chloride in the presence of an air stream. " Dehydrodiferulic acid " has consequently been made readily available, and a detailed examination has proved it to be the *dilactone* (III; R = H) of *1 : 4-dihydroxy-1 : 4-di-(4′-hydroxy-3′-methoxyphenyl)butane-2 : 3-dicarboxylic acid*. The analytical and molecular-weight values and the insolubility in sodium hydrogen carbonate solution are in agreement with this structure, and the phenolic nature is supported by the green ferric test, the formation of a *di*-p-*nitrobenzoyl* derivative, and the solubility in cold sodium hydroxide solution.

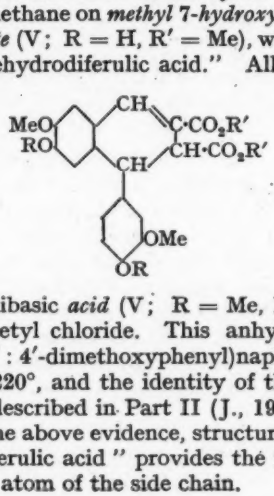
(III.) 

 (IV.)

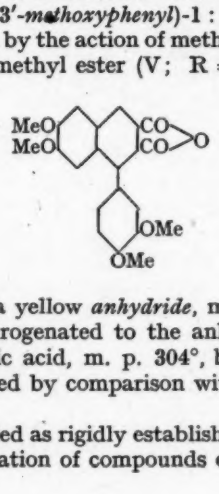
This reaction with sodium hydroxide, however, leads to considerable decomposition which was responsible for our failure to methylate the phenol with methyl sulphate in alkaline solution. The *dimethyl ether* (III; R = Me) was eventually prepared in high yield by the action of diazomethane on an acetone solution of the phenol (III; R = H). The ether gave no ferric test, and it was oxidised by alkaline potassium permanganate to veratric acid in 60% yield, thus establishing the presence of two veratryl groups in the lactone (III; R = Me). This dimethyl ether (III; R = Me) was insoluble in sodium hydrogen carbonate solution, but it dissolved with decomposition in boiling aqueous sodium hydroxide. When alcoholic sodium hydroxide was employed, the nature of the decomposition was easily traced to the production of a mixture of veratraldehyde (2 : 4-dinitrophenylhydrazone, m. p. 256°) and veratrylidenesuccinic acid (IV), m. p. 175°. The latter was identified by comparison with an authentic specimen (Stobbe, *Annalen*, 1911, **380**, 76), by conversion into the yellow anhydride (*idem*, *ibid.*), and by nitration to the *6-nitro-derivative*, m. p. 215°. The production of veratraldehyde and veratrylidenesuccinic acid from the ether (III; R = Me) represents the reversal of an aldol poly-

merisation reaction, and the degradation to veratrylidenesuccinic acid provides proof that the two ferulic units are linked at the β-carbon atoms of the side chain.

Further important evidence has been obtained from a study of the action of boiling methyl-alcoholic hydrogen chloride on the dimethyl ether (III; R = Me) and on " dehydrodiferulic acid " (III; R = H). In the former case cyclisation occurred with the production of *methyl* 6 : 7-*dimethoxy*-1-(3′ : 4′-*dimethoxyphenyl*)-1 : 2-*dihydronaphthalene*-2 : 3-*dicarboxylate* (V; R = R′ = Me). The same ester was also obtained by the action of diazomethane on *methyl* 7-*hydroxy*-6-*methoxy*-1-(4′-*hydroxy*-3′-*methoxyphenyl*)-1 : 2-*dihydronaphthalene*-2 : 3-*dicarboxylate* (V; R = H, R′ = Me), which was readily obtained by the action of methyl-alcoholic hydrogen chloride on " dehydrodiferulic acid." Alkaline hydrolysis of the methyl ester (V; R = R′ = Me) gave the



(V.)



(VI.)

corresponding dibasic *acid* (V; R = Me, R′ = H), which yielded a yellow *anhydride*, m. p. 234—235°, when treated with acetyl chloride. This anhydride was readily dehydrogenated to the anhydride (VI) of 6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)naphthalene-2 : 3-dicarboxylic acid, m. p. 304°, by heating with palladium-black at 220°, and the identity of the product was established by comparison with a specimen of (VI) synthesised as described in Part II (J., 1935, 640).

In view of the above evidence, structure (III; R = H) is regarded as rigidly established, and the formation of " dehydrodiferulic acid " provides the first example of the oxidation of compounds of the *iso*eugenol type at the β-carbon atom of the side chain.

Experimental.

α-(5-*Bromo*-4-*hydroxy*-3-*methoxyphenyl*)*propyl Alcohol*.—Ethylmagnesium iodide, prepared from magnesium (9·5 g.) and ethyl iodide (61 g.) in ethereal solution (150 c.c.), was gradually added to a solution of 5-bromovanillin (15 g.) in boiling benzene (200 c.c.). The mixture was refluxed for 1 hour, decomposed with dilute sulphuric acid, and the benzene layer was washed with sodium hydrogen sulphite solution, dried, and the solvent removed. The residual *carbinol*, m. p. 72—82°, crystallised from benzene or benzene–light petroleum (b. p. 60—80°) in clusters of needles, m. p. 88—89° (Found: C, 46·3; H, 5·2; Br, 30·5. $C_{10}H_{13}O_3Br$ requires C, 46·1; H, 5·0; Br, 30·6%), which gave a dark green ferric test.

5-*Bromo*-4-*acetoxy*-3-*methoxybenzaldehyde*, prepared by the action of acetic anhydride on 5-bromovanillin, crystallised from dilute acetic acid in colourless plates, m. p. 84° (Found: C, 44·0; H, 3·5. $C_{10}H_9O_4Br$ requires C, 43·9; H, 3·3%), and, on treatment with an ethereal solution of ethylmagnesium iodide (1·5 mols.), it was converted into an oil which yielded α-(5-bromo-4-hydroxy-3-methoxyphenyl)propyl alcohol on hydrolysis with alkali.

5-*Bromoisoeugenol* (II).—The above carbinol (4 g.) in ether (25 c.c.) was added to ethylmagnesium iodide prepared from magnesium (2·2 g.), ethyl iodide (14 g.), and ether (35 c.c.). The ether was removed, and the residue heated at 100° for 2 hours and decomposed with dilute sulphuric acid. The product, isolated with ether, was distilled at 0·6 mm.; the distillate (2·5 g.), b. p. 155—160/0·6 mm., solidified, and crystallised from light petroleum (b. p. 40—60°) in felted needles, m. p. 59—60° (Found: Br, 32·9. Calc. for $C_{10}H_{11}O_2Br$: Br, 32·9%), which gave a green ferric test (Zincke and Hahn, *Annalen*, 1903, **329**, 15, describe 5-bromo*iso*eugenol as an amorphous powder which sinters and darkens on heating). The yields are very variable in the above dehydration reaction, but other dehydrating agents, including potassium hydrogen sulphate, acetic anhydride, phosphoric oxide, anhydrous oxalic acid, and magnesium methoxide, gave inferior results.

5-*Bromo*-4-*hydroxy*-3-*methoxycinnamic Acid* (5-*Bromoferulic Acid*).—5-Bromovanillin (25 g.), malonic acid (40 g.), piperidine (1 c.c.), and pyridine (50 c.c.) were heated for 1·5 hours on the steam-bath, cooled, and poured into a solution of concentrated sulphuric acid (25 c.c.) in water (150 c.c.). The precipitate (27 g.) was collected, and crystallised from glacial acetic acid or nitrobenzene in small needles, m. p. 246° (decomp.) (Found: C, 44·4; H, 3·6; Br, 29·5. $C_{10}H_9O_4Br$ requires C, 44·0; H, 3·3; Br, 29·3%), which gave a green colour with ferric chloride. The *ethyl* ester, prepared by treatment with alcohol (25 vols.) and concentrated sulphuric acid (4 parts), crystallised from alcohol in glistening needles, m. p. 129° (Found: C, 48·0; H, 4·3; Br, 27·2. $C_{12}H_{13}O_4Br$ requires C, 47·8; H, 4·3; Br, 26·6%).

Dilactone of 1 : 4-*Dihydroxy*-1 : 4-*di*-(4′-*hydroxy*-3′-*methoxyphenyl*)*butane*-2 : 3-*dicarboxylic Acid*: " *Dehydrodiferulic Acid* " (III; R = H).—(*a*) A solution of 4-hydroxy-3-methoxycinnamic acid (40 g.) in methylated spirits (400 c.c.) was added during 15 minutes to a solution of crystalline ferric chloride (80 g.) in water (3,000 c.c.), stirred by a rapid stream of air. A chocolate-coloured precipitate gradually separated, and after 6 hours the air stream was stopped, and the reaction mixture set aside overnight. The ferric salt was collected as a paste, suspended in water (500 c.c.), heated to 70—80°, and decomposed by addition of concentrated hydrochloric acid (100 c.c.) with vigorous shaking. After cooling, the precipitate was collected, and coloured sticky material was removed by washing with ether. The residual white product, crystallised from acetone–methylated spirits, yielded plates (9 g.), m. p. 208—209° (decomp.).

(*b*) Ammonium persulphate (4·5 g.) was added to a solution of 4-hydroxy-3-methoxycinnamic acid (3·5 g.) in boiling water (200 c.c.) containing one drop of a saturated solution of ferrous sulphate. A pink colour developed, and the semi-solid product which separated on cooling crystallised from glacial acetic acid (charcoal) in plates (0·5 g.), m. p. 206—208°.

The *dilactone* (III; R = H), prepared by either method (*a*) or (*b*), separated from acetone–methylated spirits or glacial acetic acid in quadratic plates, m. p. 211° (decomp.) (Erdtman, *loc. cit.*, gives m. p. 202—205°, decomp.) [Found: C, 62·3; H, 4·6; *M* (Rast), 390. $C_{20}H_{18}O_8$ requires C, 62·2; H, 4·7%; *M*, 386]; it is almost insoluble in ether, sparingly soluble in alchol, but readily soluble in acetone or chloroform. It is readily soluble in cold sodium hydroxide, insoluble in sodium hydrogen carbonate solution, and gives a dark green ferric test. The *dinitrobenzoate* was prepared by refluxing for ½ hour a solution of the dilactone (III; R = H) (1 g.) and *p*-nitrobenzoyl chloride (1·5 g.) in dry pyridine (15 c.c.); water was added, and the precipitate (1·5 g., m. p. 253—256°) was collected and crystallised from dioxan; small, pale yellow, irregular prisms, m. p. 257—258° (decomp.) (Found: N, 4·4. $C_{34}H_{24}O_{14}N_2$ requires N, 4·1%), were obtained.

Dilactone of 1 : 4-*Dihydroxy*-1 : 4-*di*-(3′ : 4′-*dimethoxyphenyl*)*butane*-2 : 3-*dicarboxylic Acid* (III; R = Me).—An ethereal solution of diazomethane, prepared from *N*-nitrosomethylurethane (3·0 c.c.), was added to a solution of the phenolic dilactone (III; R = H) (1 g.) in acetone (50 c.c.). After 24 hours, the excess of diazomethane was destroyed by addition of a few drops of concentrated hydrochloric acid. Most of the ether was removed, the residue was taken up in chloroform, washed with water and dilute sodium hydroxide solution, and recovered. The *dilactone* (III; R = Me) crystallised from glacial acetic acid in colourless plates (0·9 g.), m. p. 207° [Found: C, 63·3; H, 5·3; *M* (Rast), 420; *M* (cryoscopically in nitrobenzene), 408. $C_{22}H_{22}O_8$ requires C, 63·7; H, 5·3%; *M*, 414]. This ether (III; R = Me), which gave a negative ferric test, could not be reduced with hydrogen in the presence of palladium–charcoal or platinic oxide. Veratric acid was obtained in 60% yield by oxidising (III; R = Me) as follows: Methyl-alcoholic potassium hydroxide was gradually added to a suspension of the ether in boiling methyl alcohol (10 vols.) until a permanent alkaline reaction to phenolphthalein was obtained. Water was then added, and the alcohol was removed by distillation. Permanganate was then added in slight excess to the warm solution, and, after the excess had been destroyed with alcohol, the mixture was filtered, and the filtrate concentrated. Acidification yielded veratric acid, which was isolated with ether and crystallised from hot water. The 6 : 6′-*dinitro*-derivative of (III; R = Me), obtained by addition of concentrated nitric acid (1·5 c.c.) in glacial acetic acid (1·5 c.c.) to a cold solution of (III; R = Me) (0·5 g.) in glacial acetic acid (5 c.c.), was sparingly soluble in the usual organic solvents, but crystallised from anhydrous formic acid in pale yellow, felted needles, m. p. 265° (decomp.) (Found: C, 52·5; H, 4·0. $C_{22}H_{20}O_{12}N_2$ requires C, 52·4; H, 4·0%).

Action of Potassium Hydroxide on the Ether (III; R = Me).—25% Methyl-alcoholic potassium hydroxide was added dropwise to a suspension of the methyl ether (1·5 g.) in boiling methyl alcohol (20 c.c.) until a permanent pink reaction was observed with phenolphthalein. 2N-Potassium hydroxide (20 c.c.) was then added, and after refluxing for 1 hour, the mixture was cooled, acidified, and extracted with chloroform. The extract was shaken with a saturated aqueous solution of sodium hydrogen carbonate and separated into an acid and a neutral fraction. Evaporation of the chloroform from the latter fraction gave an oil which was distilled at 12 mm.; the distillate, which solidified on cooling, was identified as veratraldehyde by m. p., and by preparation of the 2 : 4-dinitrophenylhydrazone, which separated from ethyl acetate in orange-red prisms, m. p. 256°, undepressed by admixture with an authentic specimen (Strain, *J. Amer. Chem. Soc.*, 1935, **57**, 760, gives m. p. 261—263°, corr.). The sodium hydrogen carbonate extract was acidified, and the acid product, isolated with chloroform, crystallised from benzene–methyl alcohol in small prisms (0·9 g.), m. p. 168—170°, raised to 175° by recrystallisation from hot water [Found: C, 58·8; H, 5·1; *M* (Rast), 270; equiv., 130. Calc. for $C_{13}H_{14}O_6$: C, 58·6; H, 5·3%; *M*, 266; equiv., 133]. The acid, identified as veratrylidenesuccinic acid (IV) by comparison with a specimen prepared by Stobbe's method (*loc. cit.*), was converted into the anhydride by refluxing with acetyl chloride; the anhydride separated from benzene either as orange prisms, m. p. 166°, containing benzene of crystallisation which was readily lost at 95°, or as unsolvated yellow prisms, m. p. 166° (Found on unsolvated material: C, 62·8; H, 4·8. Calc. for $C_{13}H_{12}O_5$: C, 62·9; H, 4·9%). 6-*Nitroveratrylidenesuccinic acid*, prepared in quantitative yield by treating the acid (0·1 g.) in glacial acetic acid (2 c.c.) with concentrated nitric acid (1 c.c.), crystallised from dilute acetic acid in pale yellow, silky needles, m. p. 215° (decomp.) (Found: C, 50·0; H, 4·0; N, 4·5; equiv., 153. $C_{13}H_{13}O_8N$ requires C, 50·1; H, 4·2; N, 4·5%; equiv., 155).

Methyl 7-*Hydroxy*-6-*methoxy*-1-(4′-*hydroxy*-3′-*methoxyphenyl*)-1 : 2-*dihydronaphthalene*-2 : 3-*dicarboxylate* (V; R = H, R′ = Me).—The dilactone (III; R = H) (1 g.) was refluxed for 2 hours with saturated methyl-alcoholic hydrogen chloride (25 c.c.). The mixture was diluted with water, and the *dimethyl* ester (V; R = H, R′ = Me), isolated with chloroform, separated from glacial acetic acid in colourless prisms (1 g.), m. p. 203—205° (Found: C, 63·1; H, 5·0; OMe, 30·0. $C_{22}H_{22}O_8$ requires C, 63·7; H, 5·3; OMe, 29·9%), which gave a green ferric test, and a green fluorescence when a little water was added to its pyridine solution.

Methyl 6 : 7-*Dimethoxy*-1-(3′ : 4′-*dimethoxyphenyl*)-1 : 2-*dihydronaphthalene*-2 : 3-*dicarboxylate* (V; R = R′ = Me).—(*a*) The methyl ether (III; R = Me) (1 g.) was refluxed for 2 hours with methyl-alcoholic hydrogen chloride (25 c.c.). The mixture was diluted with water, and the *dimethyl* ester (V; R = R′ = Me) (1 g.) was isolated with chloroform. (*b*) A solution of excess of diazomethane (1·2 g.) in ether (100 c.c.) was added to a solution of the ester (V; R = H; R′ = Me) (1 g.) in acetone (25 c.c.). After 3 days * a little concentrated hydrochloric acid was added, most of the ether was removed, and the product (1 g.) isolated with chloroform. The dimethyl ester (V; R = R′ = Me) crystallised from methyl alcohol in hard prisms, m. p. 145° (Found: C, 64·7; H, 5·9; OMe, 43·0. $C_{24}H_{26}O_8$ requires C, 65·0; H, 5·9; OMe, 42·2%), which gave a negative ferric test.

6 : 7-*Dimethoxy*-1-(3′ : 4′-*dimethoxyphenyl*)-1 : 2-*dihydronaphthalene*-2 : 3-*dicarboxylic Acid* (V; R = Me; R′ = H).—The ester (V; R = R′ = Me) was hydrolysed by refluxing for 2 hours with excess of 10% methyl-alcoholic potassium hydroxide; water was added, and the methyl alcohol removed by distillation. After acidification, the *acid* (V; R = Me; R′ = H), isolated with chloroform in quantitative yield, crystallised from ethyl acetate in hard prisms, m. p. 134° (decomp.) (Found: C, 62·5; H, 5·5. $C_{22}H_{22}O_8,\frac{1}{4}CH_3{\cdot}CO_2Et$ requires C, 62·6; H, 5·7%), containing ethyl acetate which was eliminated on heating for 1 hour at 100°; the residue had m. p. 154° (Found: C, 63·3; H, 5·3; equiv., 208. $C_{22}H_{22}O_8$ requires C, 63·7; H, 5·3%; equiv., 207). The acid (V; R = Me, R′ = H) was converted into the ester (V; R = R′ = Me), m. p. 145°, by heating with methyl-alcoholic hydrogen chloride. The *anhydride* of the acid (V; R = Me; R′ = H), prepared by the action of acetyl chloride, crystallised from glacial acetic acid in glistening yellow leaflets, m. p. 234—235° (Found: C, 66·0; H, 5·2. $C_{22}H_{20}O_7$ requires C, 66·5; H, 5·1%). The acid (V; R = Me; R′ = H) or the anhydride, m. p. 235° (0·1 g.), was heated with palladium-black (0·02 g.) at 220° for 1 hour; sublimation for 2 hours at 250—270°/0·4 mm. yielded the anhydride (VI) of 6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)naphthalene-2 : 3-dicarboxylic acid, which crystallised from nitrobenzene in pale yellow plates, m. p. 304°, undepressed on admixture with an authentic specimen (J., 1935, 640). The anhydride (VI) dissolved slowly in hot dilute sodium hydroxide solution; careful acidification yielded the corresponding dibasic acid, which separated from methyl alcohol in small colourless needles, m. p. 232—234° (decomp.), unchanged on admixture with an authentic specimen of 6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)naphthalene-2 : 3-dicarboyxlic acid.

Our thanks are due to the West Riding Education Committee for a scholarship, and to Imperial Chemical Industries Limited (Dyestuffs Division) for assistance.

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* In some experiments using less diazomethane and a shorter reaction time a product, probably *methyl* 7-*hydroxy*-6-*methoxy*-1-(3′ : 4′-*dimethoxyphenyl*)-1 : 2-*dihydronaphthalene*-2 : 3-*dicarboxylate*, crystallising from methyl alcohol in colourless prisms, m. p. 179—180° (Found: C, 64·0; H, 5·6; OMe, 37·0. $C_{23}H_{24}O_8$ requires C, 64·3; H, 5·6; OMe, 36·2%), was obtained. This alkali-insoluble compound gave a negative ferric test and on methylation with excess diazomethane in ether–acetone solution was converted into the dimethyl ester (V; R = R′ = Me), m. p. 145°.

148. *The Preparation of Some Halogenonaphthylamines, Dihalogenonaphthalenes, 2-Bromo-1-naphthol, and Related Derivatives.*

By Herbert H. Hodgson and David E. Hathway.

The facile reduction of halogenonitronaphthalenes by means of iron in neutral environment and in presence of ferrous ammonium (or ferrous) sulphate has facilitated the preparation of halogenonaphthylamines in excellent yield. Many derivatives of these amines are also described, together with 2-bromo-1-naphthol.

The ready diazotisation of nitronaphthylamines by Hodgson and Walker's procedure (J., 1933, 1620), and the prevention of diazo-oxide formation by working with the minimum of water present in the subsequent Sandmeyer reaction, has enabled a number of halogenonitro-compounds to be obtained which were formerly inaccessible, and Hodgson and Marsden's reduction method (this vol., p. 398) has brought about their conversion into the respective amines in almost quantitative yield. By these simplified processes the risk of side reactions has been reduced to a minimum. In particular, we now report the preparation of the 2-halogeno-1- and 4-halogeno-2-naphthylamines, from which several new 1 : 2- and 1 : 3-dihalogenonaphthalenes have been made, together with 2-bromo-1-naphthol and many relevant derivatives.

It is noteworthy that the m. p.'s of the 4-halogeno-2-naphthylamines show a gradual rise in the sequence Cl < Br < I but are all considerably lower than the m. p. of 2-naphthylamine; on the other hand, the m. p.'s of the isomeric 3-halogeno-1-naphthylamines exhibit a gradual rise in the sequence Cl < Br < I, being above the m. p. of 1-naphthylamine. These sequences indicate, respectively, retardation and facilitation by the halogen in 4-position of the resonance of 2-naphthylamine into the 1 : 2- and the 2 : 6-ionic resonance structures (cf. Pauling, " Nature of the Chemical Bond," Cornell Univ. Press, 1940, p. 152).

Experimental.

General Method for Reduction of 2-Halogeno-1-nitronaphthalenes.—The halogenonitro-compound (5 g.) was boiled under reflux with iron (pin dust, 10 g.) and water (100 c.c.) containing ferrous ammonium (or ferrous) sulphate (1 g.) for 1½ hours, and the mixture then steam-distilled or extracted with a solvent. 2-Chloro-1-naphthylamine (4 g.) was thus obtained in colourless needles (from alcohol), m. p. 60° (Cleve, *Ber.*, 1887, **20**, 450, and Charrier and Ferreri, *Gazzetta*, 1911, **41**, II, 726, give m. p. 56°) (Found: N, 8·0. Calc.: N, 7·9%), volatile in steam (3 g. per l.). 2-Chloroaceto-1-naphthalide crystallised from glacial acetic acid in glistening, white, rectangular plates, m. p. 192° (Charrier and Ferreri, *loc. cit.*, give m. p. 191°) (Found: N, 6·5. Calc.: N, 6·4%). *2-Chlorobenzo-1-naphthalide*, prepared by the Schotten–Baumann reaction in acetone, crystallised from alcohol (charcoal) in glistening, rectangular plates, m. p. 158° (Found: N, 5·2. $C_{17}H_{12}ONCl$ requires N, 5·0%).

2-Bromo-1-naphthylamine (yield, 4·1 g.) crystallised from aqueous alcohol in glistening needles, m. p. 65° (Found: N, 6·4. $C_{10}H_8NBr$ requires N, 6·3%), volatile in steam (2 g. per l.). Its *benzoyl* derivative, prepared as above, crystallised from aqueous alcohol in rosettes of colourless needles, m. p. 179° (Found: N, 4·3. $C_{17}H_{12}ONBr$ requires N, 4·3%), and its *acetyl* derivative crystallised from glacial acetic acid in colourless plates, m. p. 198° (Found: N, 5·4. $C_{12}H_{10}ONBr$ requires N, 5·3%).

2-Iodo-1-naphthylamine crystallised from aqueous alcohol in very pale straw-coloured needles, m. p. 85° (Found: N, 5·3. $C_{10}H_8NI$ requires N, 5·2%), which darkened on keeping; volatility in steam, 0·8 g. per l. The *hydrochloride* was obtained in colourless needles by passing dry hydrogen chloride into a benzene solution of the amine (Found: HCl, 11·6. $C_{10}H_8NI,HCl$ requires HCl, 11·5%). The acetyl derivative, prepared (m. p. *ca.* 230°) by addition of acetyl chloride to a benzene solution of the amine, decomposed with separation of iodine on attempted recrystallisation. The *benzoyl* derivative, prepared by the Schotten–Baumann reaction in acetone, crystallised from alcohol (charcoal) in colourless micro-needles, m. p. 212° (Found: N, 4·0. $C_{17}H_{12}ONI$ requires N, 3·8%).

Some Derivatives of 3-Nitro-1-naphthylamine.—*3-Nitro-1-phthalimidonaphthalene* was prepared by refluxing for 2 hours a solution of the amine (1·5 g.) and phthalic anhydride (1·3 g.) in tetralin (7 c.c.), the water formed being allowed to escape. On cooling, the phthalimide crystallised out overnight; it was dried at the pump as far as possible, and coloured impurity removed by xylene extraction (Soxhlet); it then crystallised from tetralin in rhombic plates, m. p. above 300° (Found: N, 8·8. $C_{18}H_{10}O_4N_2$ requires N, 8·8%). *3-Nitro-1-succinimidonaphthalene* was similarly prepared (yield, 1·1 g.) from the amine (1·9 g.) and succinic anhydride (1 g.); it crystallised from tetralin in rhombic plates, m. p. above 300° (Found: N, 10·4. $C_{14}H_{10}O_4N_2$ requires N, 10·4%).

3-Nitro-NN-bistoluene-p-sulphonyl-1-naphthylamine was obtained when the amine (1·5 g.) and toluene-*p*-sulphonyl chloride (4·0 g.) were ground together, and the mixture heated on the water-bath for 2 hours with water (30 c.c.) and acetone (7 c.c.), with addition of sodium carbonate when necessary to keep it alkaline. The crude naphthalide was separated and extracted with 4% aqueous sodium hydroxide (200 c.c.) at 100° for 30 minutes to remove any monosulphonyl compound. The insoluble disulphonyl compound (2·5 g.) crystallised from acetone in pale buff, rectangular plates which sintered at 249°, m. p. 257° (Found: N, 5·8. $C_{24}H_{20}O_6N_2S_2$ requires N, 5·6%).

3-Nitro-NN-diacetyl-1-naphthylamine was obtained when the monoacetyl compound (0·5 g.) was refluxed for 4 hours with a mixture of acetyl chloride (7 c.c.) and acetic anhydride (7 c.c.); the filtered solution was concentrated and deposited a greyish-white, crystalline powder; fractional crystallisation from glacial acetic acid afforded first the unchanged acetyl compound, and then the diacetyl compound in white, glistening needles, m. p. 145° (Found: N, 10·4. $C_{14}H_{12}O_4N_2$ requires N, 10·3%). Acetic anhydride alone did not effect the further acetylation. *3-Nitro-NN-dibenzoyl-1-naphthylamine* was formed when the monobenzoyl compound (1·5 g.) and benzoyl chloride (10 c.c. containing 1 c.c. of acetic anhydride) were heated together in a sealed tube for 6 hours at 200°; the product was triturated with aqueous sodium carbonate, then crystallised once from glacial acetic and twice from ethyl alcohol, the dibenzoyl derivative being obtained in yellow plates, m. p. 205° (Found: N, 7·4. $C_{24}H_{16}O_4N_2$ requires N, 7·1%).

3-Nitronaphthaleneazo-β-naphthol was made by the addition below 15° of 3-nitronaphthalene-1-diazonium sulphate (prepared from the amine by Hodgson and Walker's procedure, *loc. cit.*) to alkaline β-naphthol; it crystallised from glacial acetic acid in maroon, micro-needles, m. p. 215° (Found: N, 12·0. $C_{20}H_{12}O_3N_4$ requires N, 12·2%), that gave a deep purple colour with concentrated sulphuric acid, changing to scarlet on dilution.

4-Halogeno-2-nitronaphthalenes and -2-naphthylamines.—The nitro-compounds were obtained more conveniently from 3-nitro-1-naphthylamine than by Hodgson and Elliott's procedure (J., 1935, 1851), and were converted by the above

iron reduction method into the corresponding naphthylamines, 6 g. of nitro-compound yielding *ca.* 3·5 g. of amine. 4-Chloro-2-nitronaphthalene crystallised from alcohol in felted, lemon needles, m. p. 129° (Hodgson and Elliott, *loc. cit.*, give m. p. 127°). 4-*Chlorobenzo*-2-*naphthalide*, prepared by the Schotten–Baumann reaction in acetone, crystallised from alcohol in colourless plates, m. p. 135° (Found : N, 5·3. $C_{17}H_{12}ONCl$ requires N, 5·0%), and the *bromo*-analogue similarly formed buff micro-plates, m. p. 142° (Found : N, 4·3. $C_{17}H_{12}ONBr$ requires N, 4·3%).

Some Dihalogenonaphthalenes, and 2-*Bromo*-1-*naphthol.*—2-*Bromo*-1-*iodonaphthalene.* 2-Bromo-1-naphthylamine (2·2 g.) was suspended as the finely divided sulphate in sulphuric acid (3 c.c., *d* 1·84) and water (15 c.c.) and stirred below 10° with aqueous sodium nitrite (0·7 g.). Excess of nitrous acid was removed by urea, and the solution was then stirred into saturated aqueous potassium iodide (5 g.) below 15°. After being stirred for 4 hours, the mixture was kept overnight and then poured on ice, the precipitate washed with sodium thiosulphate, extracted with ether, the extract washed successively with 5% aqueous sodium hydroxide and thiosulphate, the ether removed from the extract, and the residue crystallised twice from ethyl alcohol, 2-*bromo*-1-*iodonaphthalene* being obtained in very pale flesh-coloured plates, m. p. 65° (0·0486 G. gave 0·0630 g. of AgBr + AgI. $C_{10}H_6BrI$ requires 0·0617 g.).

2-*Bromo*-1-*naphthol.* 2-Bromo-1-naphthylamine sulphate (3·3 g.) was diazotised as above, excess of nitrous acid removed, and the filtered solution added dropwise to boiling 50% aqueous sulphuric acid through which steam was passing (cf. Hodgson, B.P. 200,714); the colourless needles of 2-*bromo*-1-*naphthol* (0·5 g.) which separated from the steam-distillate on cooling (ice) were removed and then crystallised from light petroleum, forming rosettes of colourless needles, m. p. 45° (Found : Br, 35·6. $C_{10}H_7OBr$ requires Br, 35·9%). 4-*Benzeneazo*-2-*bromo*-1-*naphthol* crystallised from acetone in red micro-needles, m. p. 150° (Found : Br, 24·1. $C_{16}H_{11}ON_2Br$ requires Br, 24·5%), which gave a fine purple colour with concentrated sulphuric acid, turning scarlet on dilution.

1-*Chloro*-3-*bromonaphthalene.* 4-Chloro-2-naphthylamine (1·5 g.) was diazotised as for 2-nitro-1-naphthylamine (Hodgson and Walker, *loc. cit.*), and the solution stirred into one of cuprous bromide (2·5 g.) in hydrobromic acid (5 c.c., *d* 1·7); the mixture was poured on ice, the yellowish-brown precipitate of 1-*chloro*-3-*bromonaphthalene* removed, washed, dried, dissolved in benzene, the solution filtered, extracted with 5% aqueous sodium hydroxide, and the benzene layer removed, washed, and dried; on evaporation of the benzene at room temperature, 1-chloro-3-bromonaphthalene crystallised out; it recrystallised from methyl alcohol containing a little acetone in long, colourless needles, m. p. 60° (0·0864 G. gave 0·1176 g. of AgCl + AgBr. $C_{10}H_6ClBr$ requires 0·1186 g.).

1-*Chloro*-3-*iodonaphthalene* was formed when the diazonium solution, prepared as above, was stirred into a saturated solution of potassium iodide (5 g.), and was purified as for the preceding compound except for an additional extraction of the benzene solution with aqueous sodium thiosulphate; it crystallised from methyl alcohol containing acetone in rosettes of large, colourless, sabre-shaped crystals, m. p. 58° (0·0706 G. gave 0·0910 g. of AgCl + AgI. $C_{10}H_6ClI$ requires 0·0924 g.).

3-*Chloro*-1-*bromonaphthalene* was prepared from 4-bromo-2-naphthylamine (1·1 g.) by the usual Sandmeyer reaction and purified like its isomeride (above); it crystallised from methyl alcohol containing acetone in fine, colourless needles, m. p. 56° (0·0800 G. gave 0·1090 g. of AgCl + AgBr. $C_{10}H_6ClBr$ requires 0·1100 g.).

1-*Bromo*-3-*iodonaphthalene* was prepared like the 2-bromo-1-iodo-isomeride from 4-bromo-2-naphthylamine; it crystallised from ether in long, pink needles, which recrystallised from methyl alcohol containing acetone and ligroin in rosettes of colourless, sagittate crystals, m. p. 65° (0·1224 G. gave 0·1530 g. of AgBr + AgI. $C_{10}H_6BrI$ requires 0·1555 g.).

1 : 3-*Di*-*iodonaphthalene* was prepared from 4-iodo-2-naphthylamine as above, and purified by dissolution in benzene with subsequent extraction of the solution by 5% aqueous sodium hydroxide and sodium thiosulphate, after which the extracted benzene was dried and allowed to evaporate slowly at room temperature; the di-iodo-compound was deposited and, after two crystallisations from acetone containing methyl alcohol, it separated from acetone in almost colourless micro-needles, m. p. 76° (Found : I, 66·6. $C_{10}H_6I_2$ requires I, 66·8%).

The authors thank I.C.I. Ltd., Dyestuffs Division, for various gifts.

TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, May 1st*, 1944.]

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149. *The Diazotisation of 1-Amino-2-hydroxy-4-cyanonaphthalene and the Preparation of 4-Cyano-2-naphthol.*

By HERBERT H. HODGSON and STANLEY BIRTWELL.

The attempted diazotisation of 1-amino-2-hydroxy-4-cyanonaphthalene by dilution of its solution in nitrosylsulphuric acid with water gave mainly 4-cyano-1 : 2-naphthaquinone, and dilution with glacial acetic acid afforded a mixture of this quinone and 4-cyanonaphthalene-1 : 2-diazo-oxide. Solid sodium nitrite added to a glacial acetic acid solution of the above amine produced a 90% yield of 4-cyanonaphthalene-1 : 2-diazo-oxide. Boiling ethyl alcohol rapidly reduced this diazo-oxide to 4-cyano-2-naphthol.

BRADLEY and ROBINSON (J., 1934, 1484) reported that 1-amino-2-hydroxy-4-cyanonaphthalene was not diazotised when a concentrated solution of sodium nitrite was added gradually to one of the base in concentrated sulphuric acid at — 10° to — 5°. Instead, they obtained an orange-yellow solid on dilution with water which could not be coupled with resorcinol in alkaline solution. Further, the base was recovered unchanged after being stirred with an acidified solution of copper sulphate and sodium nitrite in contrast to the ready diazotisation of 1-amino-2-naphthol-4-sulphonic acid (D.R.-P., 171,024; Friedländer, vol. 8, p. 640).

The authors have now established that excess of nitrosylsulphuric acid converts 1-amino-2-hydroxy-4-cyanonaphthalene in the presence of water into 4-cyano-1 : 2-naphthaquinone in *ca.* 89% yield. Bradley and Robinson's orange-yellow solid was then found to be this quinone in an impure state, and its identity was established by condensation with *o*-phenylenediamine to form 3-cyano-1 : 2-benzphenazine. When, however, the theoretical amount of nitrosylsulphuric acid necessary for diazotisation was used, the resulting product contained some 4-*cyanonaphthalene*-1 : 2-*diazo-oxide* mixed with the above quinone. In Bradley and Robinson's experiment, therefore, the excess of nitrous acid (or perhaps the nitrosylsulphuric acid itself) had behaved as

an oxidising agent; those authors readily obtained 4-cyano-1 : 2-naphthaquinone from the 1-amino-2-hydroxy-4-cyanonaphthalene by ice-cold oxidation with chromium trioxide in concentrated sulphuric acid.

We have found that the nitrosylsulphuric–glacial acetic acid procedure (Hodgson and Walker, J., 1933, 1620) materially increased the amount of diazo-oxide in the above mixture, and thereby diminished the oxidation which had predominated in the presence of water. As expected from this result, it was found that complete diazotisation was effected by the addition of solid sodium nitrite to a solution of 1-amino-2-hydroxy-4-cyanonaphthalene in glacial acetic acid only, and at room temperature. The yield of 4-cyanonaphthalene-1 : 2-diazo-oxide was 90% (cf. Hodgson and Foster, J., 1942, 30, for similar diazotisations of arylazo-β-naphthylamines).

The above gradual variation in the action of nitrous acid on a readily oxidisable *o*-aminonaphthol, *viz.*, in concentrated sulphuric acid (no action), aqueous sulphuric acid (almost complete oxidation), sulphuric–glacial acetic acid (oxidation with some diazotisation), and glacial acetic acid (almost complete diazotisation), is of interest, especially as it seems to run parallel with the gradual decrease of ionisation of the nitrous acid in the sequence of media.

4-Cyanonaphthalene-1 : 2-diazo-oxide was easily reduced by boiling alcohol to 4-cyano-2-naphthol, but admixed with some azo-by-product formed by a slight amount of coupling of the diazo-oxide with the cyanonaphthol. This impurity was removed as an insoluble barium lake by addition of barium chloride to the solution of the reaction mixture in aqueous alkaline hydroxide.

Experimental.

1-*Amino*-2-*hydroxy*-4-*cyanonaphthalene*.—This was prepared according to Bradley and Robinson (*loc. cit.*), and the crude hydrochloride was employed without further purification in the experiments now described. When sodium cyanide was used instead of potassium cyanide, slightly lower yields were obtained.

4-*Cyano*-1 : 2-*naphthaquinone*.—1-Amino-2-hydroxy-4-cyanonaphthalene (1·8 g.), obtained from the hydrochloride by treatment with sodium acetate solution, was dissolved below 10° in sulphuric acid (10 c.c., *d* 1·84) and stirred below 10° into a solution of sodium nitrite (1·75 g., 2·5 equivs.) in sulphuric acid (15 c.c., *d* 1·84). After an hour's stirring, the mixture was poured on ice, whereupon a copious evolution of gas occurred; the yellow-brown precipitate of 4-cyano-1 : 2-naphthaquinone was collected, washed, and dried; m. p. 170°; yield, 1·6 g. (89%). It separated from water in red-brown crystals, m. p. 175°, and from benzene in orange prisms, m. p. 175—176° (Bradley and Robinson, *loc. cit.*, give m. p. 175—176°) (Found : N, 7·8. Calc. for $C_{11}H_5O_2N$: N, 7·7%). Hot glacial acetic acid solutions of the above compound and *o*-phenylenediamine, when admixed, gave an immediate precipitate of 3-cyano-1: 2-benzphenazine, which recrystallised from glacial acetic acid in yellow needles, m. p. 247° (Bradley and Robinson give m. p. 247°) (Found : N, 16·6. Calc. : N, 16·5%).

4-*Cyanonaphthalene*-1 : 2-*diazo-oxide*.—Powdered 1-amino-2-hydroxy-4-cyanonaphthalene hydrochloride (13·2 g.) was added portionwise to a solution of anhydrous sodium acetate (6 g.) in glacial acetic acid (60 c.c.) at about 40°. The mixture was then cooled to room temperature, powdered sodium nitrite (5·0 g.) added, and the whole stirred for 30 minutes at about 30°, this temperature being maintained by external cooling. When the reaction was completed, the mixture was externally cooled by ice, so that as much as possible of the 4-cyanonaphthalene-1 : 2-diazo-oxide crystallised out (together with some sodium acetate and chloride). The brown precipitate was then removed, washed successively with a little glacial acetic acid and with cold water, its colour then changing to a brighter yellow; yield, 7·0 g.; m. p. 144° (decomp.). The mother-liquors, when diluted with ice and water, afforded a further 3·0 g., m. p. 138°; total yield, 10 g. (85%). 4-*Cyanonaphthalene*-1 : 2-*diazo-oxide* crystallised from water in bright yellow needles, m. p. 147·5° (slow decomp.) (Found : N, 21·7. $C_{11}H_5ON_3$ requires N, 21·5%). It coupled readily with alkaline phenols and naphthols, evolved nitrogen when treated with alcohol and zinc dust, and decomposed on exposure to sunlight. 2-*Hydroxy*-4-*cyano*-1-*naphthaleneazo*-β-*naphthol* was obtained in 90% yield when the above diazo-oxide (0·4 g.) was added to a solution of β-naphthol (0·4 g.) in alcohol (10 c.c.) at 0° into which 20% aqueous sodium hydroxide (2 c.c.) was subsequently stirred. The deep purple solution when acidified with dilute acid gave the azo-compound, which crystallised from toluene or cellosolve in dark brown or black needles with a green reflex, m. p. 250° (decomp.) (Found : N, 12·65. $C_{21}H_{12}O_2N_2$ requires N, 12·4%).

4-*Cyano*-2-*naphthol*.—The above diazo-oxide (6·9 g., 0·035 g.-mol.) was heated under reflux with ethyl alcohol (175 c.c.) for 2 hours, after which the alcohol was recovered by distillation, and the residue extracted cold with 2% aqueous sodium hydroxide (70 c.c.), the filtered extract being diluted with water to 150 c.c., and stirred with an aqueous solution of hydrated barium chloride (4·2 g.). The filtered solution, when acidified at this stage, gave a clean, though tarry product, and it was consequently diluted to 500—600 c.c., then heated to boiling (with norit), neutralised with hydrochloric acid, and filtered; on cooling, 4-*cyano*-2-*naphthol* crystallised in cream-coloured needles (1·7 g.), m. p. 125—136°. Repetition of the extraction of the above residue afforded a further 1·0 g., m. p. 123—127°, and the evaporation of the mother-liquor of a third extraction produced 0·3 g.; total yield, 3·0 g. (57%). 4-Cyano-2-naphthol crystallised from benzene and aqueous 30% methyl alcohol in colourless parallelepipeds, m. p. 138° (Found : N, 8·4. $C_{11}H_7ON$ requires N, 8·3%). Its *acetate*, prepared by refluxing it for 30 minutes with acetic anhydride, crystallised from 30% aqueous methyl alcohol (charcoal) in colourless parallelepipeds, m. p. 84° (Found : N, 6·7. $C_{13}H_9O_2N$ requires N, 6·6%).

4-*Cyano*-2-*methoxynaphthalene*, prepared by treating the naphthol with methyl sulphate in 10% aqueous sodium hydroxide, crystallised from methyl alcohol in colourless needles, m. p. 103° (Found : N, 7·2. $C_{12}H_9ON$ requires N, 7·1%). 1-*Benzeneazo*-4-*cyano*-2-*hydroxynaphthalene*, prepared by coupling diazotised aniline with alkaline 4-cyano-2-naphthol, crystallised from glacial acetic acid in small needles, m. p. 206° (Found : N, 15·4. $C_{17}H_{11}ON_3$ requires N, 15·3%).

The authors thank Imperial Chemical Industries Ltd., Dyestuffs Division, for various gifts.

Technical College, Huddersfield. [*Received, May* 23*rd*, 1944.]

150. *Some Observations on the Photochemistry of Fluorescent Substances. Part I. The Quenching of Fluorescence by Nitric Oxide and the Photochemical Formation of Nitroxides.*

By H. Weil-Malherbe and J. Weiss.

The quenching of the fluorescence of polycyclic hydrocarbons in solution by nitric oxide is described and discussed. In character and extent it is analogous to the effect of oxygen. An attempt was made to isolate stable products of the photochemical reaction between hydrocarbons and nitric oxide, but owing to the apparently great instability of the primary " photo-nitroxides " only a few milligrams of several nitrogenous products were obtained in crystalline form.

It has been suggested that the primary process of fluorescence quenching in solution by foreign substances is in many cases due to an electron transfer between the excited molecule and the quenching substance (Weiss, *Trans. Faraday Soc.*, 1938, **34**, 451; 1939, **35**, 48; Carter and Weiss, *Proc. Roy. Soc.*, 1940, *A*, **174**, 351; *Nature*, 1943, **152**, 176). Some aspects of this interpretation have also been confirmed by work on certain solid phosphors (Lewis *et al.*, *J. Amer. Chem. Soc.*, 1941, **63**, 3005; 1943, **65**, 2419). In general, the sequence of reactions can be represented by the following equations (A = fluorescent molecule, B = quenching agent):

Light absorption	$A + h\nu \longrightarrow A^*$ (excited molecule)	(1)
Fluorescence emission	$A^* \longrightarrow A + h\nu'$	(2)
Quenching	$A^* + B \longrightarrow (A^*B)$	(3)

with a subsequent electron transfer between A* and B resulting in either (A^+ and B^-) or (A^- and B^+). Thus the increased reactivity of the molecule in the excited as compared with the ordinary state manifests itself in one of two ways: (*a*) An electron transfer from A* to B, favoured by the decrease of the ionisation potential of the excited dye, approximately corresponding to the optical excitation energy ($h\nu$); this is the mechanism in the case of polycyclic hydrocarbons, chlorophyll, trypaflavine adsorbates, etc. (where there are non-localised π-electrons in the conjugated systems of double bonds), if the quenching agent has electron-accepting properties (*e.g.*, oxygen). (*b*) An electron transfer from B to A* owing to the increased electron affinity of the excited molecule (or ion), *e.g.*, in the case of methylene-blue and other dye cations, if the quencher has electron-donating properties (*e.g.*, the ferrous ion).

The quenching of fluorescence by oxygen is represented by (4) and the regeneration of the initial state by (5):

$$A^* + O_2 \longrightarrow A^+ + O_2^- \quad (4)$$
$$A^+ + O_2^- \longrightarrow A + O_2 \quad (5)$$

If oxygen is removed by evacuation, or replaced by an atmosphere of pure nitrogen, the reaction is reversible and the fluorescence is restored. This was first found by Kautsky for trypaflavine gel and chlorophyll solutions (*Ber.*, 1931, **64**, 2677), and later also for aromatic hydrocarbons by Bowen and Williams (*Trans. Faraday Soc.*, 1939, **35**, 765), Weil-Malherbe and Weiss (*Nature*, 1942, **149**, 471), and Miller and Baumann (*J. Amer. Chem. Soc.*, 1943, **65**, 1540).

It was to be expected that other gases with an electron affinity would also have the ability to quench fluorescence. A number of gases were investigated by Miller and Baumann (*loc. cit.*). Sulphur dioxide proved to be a much more potent quencher than oxygen, possibly owing to its higher solubility in light petroleum. It is, however, noteworthy that polycyclic hydrocarbons form molecular compounds with sulphur dioxide in the liquid (cf. Weiss, J., 1942, 245), so it is possible that the quenching by sulphur dioxide is not a photochemical, but a dark reaction, though there is at present some difficulty in deciding between the two mechanisms.

We investigated a number of gases and found a strong and reversible quenching effect by nitric oxide (*Nature*, 1943, **151**, 449), the extent (Table I) being very similar to that which we found with oxygen (*ibid.*, 1942, **149**, 471); it varies somewhat from one hydrocarbon to another and also with the solvent, probably owing to differences of solubility. An exception to the analogy with oxygen is observed in the case of rubrene, the fluorescence of which is inhibited to the extent of 68% and 5% by oxygen and nitric oxide, respectively. The reversibility is incomplete in the case of 20-methylcholanthrene, but is almost quantitative with the other compounds investigated.

Although the fluorescence quenching by oxygen and other gases is completely reversible, it is well known that anthracene derivatives, on prolonged irradiation, form stable peroxides of the type AO_2 (cf. Dufraisse, *Bull. Soc. chim.*, 1939, **6**, 422; Cook and Martin, J., 1940, 1125), thus supporting the proposed mechanism of the quenching reaction. The stabilisation of the primary bimolecular association product is in general brought about by a " third body " according to:

$$A^+ + O_2^- (+ M) \longrightarrow AO_2 (+ M) \quad (M = \text{" third body "}) \quad (6)$$

(see Weiss, *Trans. Faraday Soc.*, 1942, **38**, 366). In solution, every collision between two solutes is practically a ternary collision, but probably some molecules are more efficient for the stabilisation of the reaction product than others.

The yield also depends on the extent of secondary photochemical decomposition of the peroxide. The particularly good yields of photo-oxides, when carbon disulphide is used as the solvent, may be explained by

the strong absorption of the wave-lengths below 3800 A. by this solvent, which thus acts as a light filter for the short wave-lengths which would otherwise be absorbed by the photo-oxides.

In our attempts to isolate a stable product of the photochemical reaction between polycyclic hydrocarbons and nitric oxide, we first used carbon disulphide as solvent. The results were, however, no more favourable than when the solvent was hexane, and this was used in all subsequent experiments. The hydrocarbons chosen were anthracene and 9 : 10-dimethyl-1 : 2-benzanthracene, as it is known that *meso*-substituted anthracene derivatives are especially reactive in addition reactions of the kind investigated. Under the conditions employed, about 80% of hydrocarbon was recovered unchanged after an irradiation of 4—5 hours in an atmosphere of nitric oxide. The remainder was a mixture which by chromatographic adsorption analysis was resolved into approximately 30 components. The distribution of the various fractions and the general character of the chromatogram were very similar with both hydrocarbons. The bulk of the reaction products was made up of nitrogen-free compounds. In the anthracene experiment a considerable amount of anthraquinone was isolated. Other nitrogen-free compounds, from their high adsorption affinities, high melting points, and insolubility, appeared to be polymerisation products. One crystalline fraction which was isolated from the deposit that had formed from anthracene on the walls of the vessel during irradiation, was judged by its appearance, slight solubility, and melting point to be dianthracene. As we were mainly interested in the nitrogenous compounds, the nitrogen-free substances were not further investigated. It is probable, however, that they originated, at least in part, from " photo-nitroxides " by secondary decomposition, for irradiation under similar conditions in an atmosphere of pure nitrogen caused the disappearance of only 5% of hydrocarbon.

The yield of nitrogen-containing compounds (usually deep yellow) amounted to only a few mg. in each case. If we formulate the photo-nitroxides as A(NO) (A = hydrocarbon) the calculated nitrogen content of the primary product from 9 : 10-dimethyl-1 : 2-benzanthracene is 4·9%, and that from anthracene 6·7%. The nitrogen-content of most fractions was higher than the calculated values, indicating either the entry of more than one nitrogen-containing group into the molecule or a splitting of the ring structure with loss of carbon. From a preliminary experiment with anthracene, which was worked up immediately after irradiation, a substance was isolated with N, 5·72%. Its adsorption affinities, as judged by its position on the alumina column, were closer to those of anthracene than any of the other reaction products. As this substance was absent from the pooled irradiated solutions of later experiments, which were kept in the laboratory for some time, it must be labile. These properties are consistent with the assumption of its being identical with the primary photo-nitroxide. The somewhat low nitrogen content is probably due to contamination with unchanged anthracene, from which it is not easily separated by chromatography. The substance is of deep orange colour; it absorbs in the ultra-violet from 3500 to 4000 A., with a peak at 3800 A., and again at lower wave-lengths with a maximum at about 2500 A. There is thus an overlapping of the absorption spectra of the hydrocarbon and the (presumed) photo-nitroxide, conditions which are very unfavourable for the preparation of the latter, in contrast to the sufficiently wide gap between the absorption spectra of the photo-peroxides and their parent hydrocarbons, which renders possible the stabilisation of the former.

Experimental.

Nitric oxide, prepared by addition of 40% sodium nitrite from a dropping funnel to a solution of 500 g. of hydrated ferrous sulphate in 1000 ml. of 10% sulphuric acid, was passed through two wash-bottles of concentrated sulphuric acid and two of 50% potassium hydroxide, and finally dried over phosphoric oxide. The components of the apparatus were joined by fusion or by ground-glass joints. After assembly, the apparatus was thoroughly rinsed out with pure nitrogen. At the end of an experiment the flask used for the generation of nitric oxide and the train of wash-bottles and drying tube were left filled with nitric oxide and shut off by a tap. The generating flask was provided with an outlet through which waste solution could be drawn off and replaced by fresh ferrous sulphate solution without admission of air. Before the vessel containing the irradiated solution was disconnected, the nitric oxide was quantitatively displaced by nitrogen.

Fluorescence measurements were carried out in the manner previously described (Weil-Malherbe, J., 1943, 303). Three readings were taken in each case : one in nitrogen, a second in nitric oxide, and a third again in nitrogen. Five minutes were allowed for saturation with the particular gas before the reading.

For the preparative experiments a rectangular, fused quartz cell of about 150 ml. capacity was used at a distance of about 40 cm. from a Hanovia mercury lamp. During irradiation the vessel was cooled by running water.

Examples of Preparative Irradiation Experiments.—(1) 9 : 10-*Dimethyl*-1 : 2-*benzanthracene.* 300 Mg. of hydrocarbon were dissolved in 100 ml. of hexane and irradiated in an atmosphere of nitric oxide for 4 hours. The slightly yellow solution was then twice extracted with 25 ml. of 2N-sodium hydroxide. The alkaline extract was immediately acidified, and repeatedly extracted with benzene. Both the hexane and the benzene solution were dried over calcium chloride and separately chromatographed on alumina columns. The hexane solution was poured on a column of 10 g. of alumina and treated with a series of solvents of increasing eluant power, *viz.*, hexane (1000 ml.), benzene–light petroleum (1 : 4; 100 ml.), benzene (10 + 20 ml.), ethyl acetate (10 + 15 ml.), methanol (100 ml.), and methanol with 10% acetic acid (100 ml.). A number of bands were formed, recognisable by their colour (yellow, orange, or brown) or fluorescence. Fractionation of the eluate was carried out according to the progress of the bands as observed in filtered ultra-violet light. The two benzene and the two ethyl acetate fractions were again separately chromatographed on smaller alumina columns and were thus resolved into 8 apparently homogeneous fractions. The fractions were then concentrated until crystallisation began or to dryness. The first two fractions consisted of unchanged hydrocarbon (235 mg.). From the second benzene fraction 1·3 mg. of orange needles (Found : N, 6·6%) were isolated. In the corresponding fraction of another experiment the nitrogen content was 6·50%. The first ethyl acetate fraction yielded 5 mg. of lemon-yellow crystals (Found : N, 5·3%). The second ethyl acetate fraction yielded 1 mg. of colourless, nitrogen-free crystals, m. p. 180° (uncorr.). From the methanol fraction 7·2 mg. of colourless, nitrogen-free crystals, insoluble in benzene, soluble in ethanol, were obtained; m. p. > 300°. The last fraction gave 5 mg. of difficultly soluble, amorphous or microcrystalline substance; this did not melt below 300° and did not contain nitrogen. All other fractions yielded only traces of oily smears.

The alkali-soluble fraction, after chromatographic adsorption and fractional elution, was resolved into a number of fractions which left only oily residues, except that the methanol fraction afforded 8 mg. of colourless crystals; these had m. p. > 300° and were nitrogen-free.

(2) *Anthracene.* 3·0 G. were dissolved in 1500 ml. of hexane and irradiated for 4 hours in batches of about 100 ml. The irradiated solutions were united and worked up together. During the irradiation a dark deposit formed on the walls of the vessel. It consisted of unchanged anthracene, which was washed out with hot hexane, and of more difficultly soluble material. It was treated first with hot benzene and then with hot ethanol. The united benzene washings were evaporated, the residue repeatedly extracted with hot hexane, and the hexane-insoluble part recrystallised from hot benzene; 65 mg. of colourless, nitrogen-free crystals (?dianthracene) were obtained, m. p. 267° (uncorr.) on rapid heating.

The main hexane solution was repeatedly extracted with 100-ml. portions of 2N-sodium hydroxide, the extract acidified, and extracted with 5 portions of 150 ml. of benzene. Hexane and benzene solutions were dried over calcium chloride. The hexane solution was chromatographed on a column of 100 g. of alumina, 2·5 × 21 cm. Elution proceeded on the lines detailed above, the following fractions being collected: hexane (2000 ml.), benzene–light petroleum (1 : 4; 1000 ml.), benzene (300 + 500 ml.), ether (1000 + 300 + 200 ml.), ethyl acetate (200 + 80 + 300 ml.), methanol (200 + 150 ml.). The column was then removed and divided into 3 parts, each being extracted several times with a total of about 400 ml. of hot methanol containing 10% acetic acid. With the exception of the hexane fraction, which contained only unchanged anthracene, and of the several methanol fractions, all intermediate fractions were evaporated, redissolved in either light petroleum or benzene, and again chromatographed on smaller columns (about 5 g. of alumina). Fractions from different columns which seemed identical were combined, and chromatography was repeated until the fractions were chromatographically homogeneous. On evaporation, 7 fractions yielded weighable amounts of crystalline products (Nos. 2—8, Table II), whereas several others either left only oily residues, usually dark, or too little crystalline material for investigation.

TABLE I.

Reversible quenching of fluorescence in nitric oxide.

Solute.	Concn., μg./5 ml.	Solvent.	Deflection (arbitrary units). N_2 (1st reading).	NO.	N_2 (2nd reading).	Quenching, %.
3:4-Benzpyrene	7·5	Hexane	353	23	345	93·5
	6	Decalin	352	82	344	76·7
	6	Ethanol	285	38	285	86·7
20-Methylcholanthrene	50	Hexane	243	24	170	90·0
	50	Decalin	404	90	350	77·7
	50	Ethanol	360	59	327	83·6
Anthracene	500	Hexane	315	92	310	70·8
	500	Decalin	355	213	355	40·0
	500	Ethanol	307	138	304	55·0
1:2-Benzanthracene	300	Hexane	270	16	266	94·1
	300	Ethanol	320	31	317	90·3
9:10-Dimethyl-1 : 2-benz-anthracene	150	Hexane	395	36	386	90·9
	150	Ethanol	388	60	360	84·5
1:2:5:6-Dibenzanthracene	500	Hexane	100	15	96	85·0
Naphthacene	Sat.	Hexane	62	18	56	71·0
Rubrene	300	Hexane	256	239	261	6·5
	300	Ethanol	140	133	140	5·0
Ethylchlorophyllide	50	Ethanol	30	21	30	30·0

TABLE II.

Fractions isolated after irradiation of anthracene in an atmosphere of nitric oxide.

No.	Yield (mg.).	M. p. (uncorr.).	Appearance.	Fluorescence of solution.	Reaction with conc. H_2SO_4.	N, %.
1	9·0	139°	Orange needles	—	Rust-brown colour	5·72 ‡
2	2·0	261	Cream-coloured needles	Brilliant light blue	Yellow colour	0
3	36·5	279 *	Pale yellow needles	—	Yellow colour	0
4	1·5	276 (sint. 240°)	Cream-coloured needles	White	Yellow colour	?
5	6·1	244	Colourless plates (*ex* benzene)	Bright blue	No colour	8·35
6	7·0	108	Yellow needles (*ex* benzene)	Weak yellow	Ruby-red colour	14·9
7	10·3	163	Yellow prisms (*ex* ethanol)	—	Purple colour	10·55 †
8	6	227 (decomp.) (sint. 188°)	Colourless cubes (*ex* ethanol)	—	No colour	0
9	180	>300	Colourless cubes (*ex* ethanol)	Weak grey-blue	No colour	0
10	28	>300	Colourless plates (*ex* ethanol)	Blue	Yellow colour	0
11	67	>300	Colourless, pale yellow crystals (octahedra, hexagons, stars like ice crystals, and various other forms (*ex isobutanol*)	Weak greyish	Effervescence	0
12	0·5	>300	Yellow needles (*ex* ether)	Yellow	Red colour	?
13	68	>300	Colourless needles or prisms in comb-like or fishbone-like arrangement (*ex* ethanol)	—	No colour	0

* M. p. of specimen of anthraquinone, 279°; mixed m. p. 279° (uncorr.).

† Found: C, 42·6; H, 4·87. Calc. for $C_{14}H_{19}O_{10}N_3$: C, 43·1; H, 4·92; N, 10·8%. U.V. absorption: band in region of 2700 A.

‡ U.V. absorption: maxima at 2500 and 3800 A.

A total of 2·52 g. of anthracene was recovered unchanged. The bulk was contained in the hexane fraction, but some of the later fractions contained small amounts. It was always the most weakly adsorbed constituent.

No crystalline products were obtained from either of the two methanol eluates. A fairly large crop of crystals was isolated from the methanol–acetic acid eluate of the lowest third of the column (Table II, No. 9). The extracts of the middle and the top third of the column left amorphous residues which could be redissolved only with great difficulty. They were extracted with large volumes of hot *iso*butanol, from which by fractional crystallisation a number of fractions were obtained; apart from differences in their microscopic appearance, these had similar properties, notably an effervescence on addition of concentrated sulphuric acid. As they did not contain nitrogen, they were not further investigated and are combined in Table II as fraction No. 11.

Fractions 1—11 (Table II) were all obtained from the alkali-insoluble fraction; they are arranged in the order of increasing adsorption on the alumina column. Fraction No. 1, which immediately followed the anthracene on the column, was absent when the united solutions from the large-scale experiment were worked up. It was actually isolated in a preliminary experiment in which 700 mg. of anthracene, dissolved in 150 ml. of hexane, were irradiated for 4 hours; at the end of the experiment 610 mg. of anthracene were recovered unchanged.

Chromatography of the alkali-soluble fraction yielded two crystalline products: fraction No. 12 which crystallised out from an ether eluate, and fraction No. 13 obtained from a methanol–10% acetic acid eluate. A number of other eluates left only oily residues.

Irradiation of 9 : 10-*Dimethyl*-1 : 2-*benzanthracene in an Atmosphere of Nitrogen.*—200 Mg. of hydrocarbon, dissolved in 80 ml. of hexane, were irradiated in pure nitrogen for 5 hours, chromatographed, and unchanged hydrocarbon recovered (191 mg.). The residue of the ethyl acetate fraction of the eluate was 8·5 mg. of a dark, oily mass, partly soluble in light petroleum. On spontaneous evaporation, a trace of colourless crystals was deposited from the light petroleum solution.

The dimethylbenzanthracene and various other hydrocarbons used in these experiments were kindly supplied by Prof. J. W. Cook, F.R.S., to whom we wish to express our indebtedness.

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151. *Some Observations on the Photochemistry of Fluorescent Substances. Part II. Concentration Quenching (Self-quenching) of Fluorescence.*

By J. WEISS and H. WEIL-MALHERBE.

The concentration quenching of several polycyclic hydrocarbons and of ethylchlorophyllide has been investigated in various solvents in an atmosphere of pure nitrogen and in the absence of foreign quenching substances.

The primary photochemical process of self-quenching is represented by an interaction between excited and normal molecules, and the hyperbolic quenching equation was found to be valid in all the cases investigated.

The relation between self-quenching and the photochemical formation of dimers has been discussed in detail. In photo-sensitised oxidations with ethylchlorophyllide self-quenching effects are of great importance, as the lifetime of the excited chlorophyll molecule is largely dependent on the concentration quenching even in the presence of other quenching substances.

IT is well known that many substances show appreciable luminescence only in molecular dispersion, and that concentrated solutions of fluorescent substances often show little or no fluorescence; on the other hand, dilute solutions, and especially those in highly viscous media, show a greatly increased fluorescence yield which sometimes reaches values approaching unity (cf. Vavilov, *Z. Physik*, 1925, **31**, 750; Banow, *ibid.*, 1929, **58**, 811; Lewschin and Vinokurow, *Physikal. Z., U.S.S.R.*, 1936, **10**, 10). In all these cases there is no indication of any appreciable interaction between the molecules of the solvent and those of the fluorescent substance, the absorption spectrum of which is also only slightly changed or not changed at all. This leads to the conclusion that the fluorescence yield depends on an interaction of the molecules of the fluorescent substance with each other.

It is obvious that the phenomenon of self-quenching cannot be due to a reabsorption of fluorescence radiation, because the exciting radiation would be absorbed in a still thinner layer and one should observe surface fluorescence, which is not the case.

The importance of concentration quenching has been emphasised by Pringsheim (*Trans. Faraday Soc.*, 1939, **35**, 31), who showed that it is not due to (i) energy (resonance) transfer between the excited and unexcited molecules, as had been suggested by Perrin (*Ann. Physique*, 1929, **12**, 147), or to (ii) the simple formation of (non-fluorescent) associated molecules, because the lifetime of the excited molecules is in fact shortened.

It is clear that " pure " self-quenching can only be studied in the absence of any other foreign quenching substances such as oxygen (Weil-Malherbe and Weiss, *Nature*, 1942, **149**, 471). This condition has often not been fulfilled in previous work. The experiments now reported on polycyclic hydrocarbons and on ethylchlorophyllide (herein briefly referred to as the " dyes ") were carried out in an atmosphere of pure nitrogen, and it was ascertained that under these conditions the fluorescence efficiency was practically independent of the solvent used (Weil-Malherbe and Weiss, *loc. cit.*).

If fluorescence intensity is plotted against concentration, a characteristic curve is obtained (*idem, ibid.*). At very low concentrations only a small fraction of the incident radiation is absorbed; in this region, absorption increases linearly with increasing concentration and self-quenching is practically absent. Here the fluorescence intensity is proportional to the primarily absorbed light intensity (Beer's law). With increasing concentration the fluorescence intensity reaches a maximum, corresponding to the total (maximum) absorption of the incident irradiation which in all these cases is kept constant throughout an experiment. In the absence of concentration

quenching, the fluorescence intensity should therefore remain constant. Actually, the fluorescence yield gradually decreases with increasing concentration of the dye owing to self-quenching. From this part of the curves certain deductions can be drawn about the nature of the self-quenching process, as shown below.

The processes of light absorption and fluorescence emission are described by equations (1) and (2) (Part I, preceding paper). The equation for the self-quenching, in analogy to equation (3) (Part I), is represented by (3*a*) (A = " dye," A* = excited " dye ") :

$$A^* + A \longrightarrow (A^+A^-) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3a)$$

(reverse process) $A^+ + A^- \longrightarrow 2A \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$

(stabilisation reaction) $A^+ + A^- (+ M) \longrightarrow A_2 (+ M) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$

The stabilisation of the primary products leads to the photochemical formation of a dimer (reaction 8). These equations are also in accord with Weigert's observations (*Naturwiss.*, 1927, **15**, 124) on anthracene solutions, in which the relative decrease of fluorescence is accompanied by an increase in the photochemical formation of dianthracene.

From reactions (1), (2) and (3*a*) one obtains for the fluorescence yield in the stationary state (cf. Weiss, *Trans. Faraday Soc.*, 1939, **35**, 48) :

$$\gamma = I/I_{abs.} = 1/\{1 + (k_{3a}/k_2)[A]\} \quad . \quad . \quad . \quad (9)$$

where $I_{abs.}$ and I are, respectively, the absorbed and the fluorescent light intensity, $\tau_0 = 1/k_2$ is the mean lifetime of the excited " dye " in the absence of any external quenching, and k_{3a} the (bimolecular) rate constant of reaction (3*a*). For total absorption of the (constant) primary radiation (*i.e.*, for $I_{abs.} = I_0 = \text{const.}$) one obtains for the decreasing part of the fluorescence curve the equation

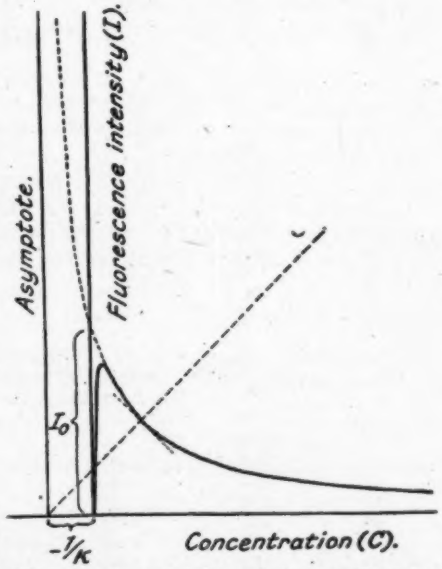
$$\gamma = I/I_0 = 1/(1 + \kappa c) \quad . \quad . \quad . \quad . \quad (10)$$

where $\kappa = \tau_0 k_{3a}$, and [A] is identified with the total concentration (c) of the dye, because $\{c - [A^*]\}$ is not very different from the total concentration.

Equation (10) can be written as

$$I\xi = I_0(1/\kappa) \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

where $\xi = c + 1/\kappa$, and this shows that the curve of decreasing fluorescence represents a rectangular hyperbola, one asymptote being the c-axis and the other parallel to the I-axis at a distance $c_{\xi=0} = -1/\kappa$ from the origin. The constant κ of equation (10) can thus be deduced graphically from the experimentally determined fluorescence curve, as is shown in the figure, which is self-explanatory.



Schematic representation of the graphic determination of the quenching constant (κ) from the experimentally determined self-quenching hyperbola (fully drawn curve).

The fluorescence intensities I (in arbitrary units) have been measured photoelectrically (see Experimental) for a number of substances at constant intensity of the incident radiation. The results are given in Tables I and II. All experiments were carried out at room temperature (20°).

From the value of κ determined by the above graphical method, the fluorescence yield (γ) can be calculated according to equation (10). These values are given in col. 4 of Table I. In the case of complete and constant absorption of the incident radiation of intensity I_0, these calculated values can be compared with the values derived from I/I_0 (col. 3). The value of I_0 in the same arbitrary units is given by the point of intersection of the hyperbola with the I-axis (see fig.), as follows directly from equation (11). The agreement is in many cases as good as can be expected.

Discussion.—The values of κ for different hydrocarbons and for ethylchlorophyllide are summarised in Table II. Two substances which have been found to have only a small self-quenching effect have also been included. As the mean lifetime of the fluorescent state in all these cases is presumably of the same order of magnitude ($\tau_0 \sim 10^{-8}$ sec.), the values of κ given on p. 546 are proportional to the actual rate constant of the self-quenching reaction (3*a*), as follows from equation (10). Whereas the self-quenching constants (κ) for the polycyclic hydrocarbons are of the order of 100 or smaller, that for ethylchlorophyllide is about 2000 times greater.

The self-quenching equation is essentially the same as the well-known equation of Stern and Volmer, although it is derived from a different physical point of view; it is identical with the exponential relationship proposed by Perrin (*loc. cit.*) and others if κc is small compared with unity, for in this case equation (10) can also be written as :

$$\gamma \sim \varepsilon^{-\kappa c} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

However, there is also some further support for the hyperbolic relationship from the experiments on the photochemical formation of dianthracene and from photosensitised oxidations with ethylchlorophyllide.

TABLE I.

Concentration quenching of hydrocarbons and ethylchlorophyllide.

$c \times 10^4$ (mol./l.).	I.*	γ. Obs. I/I_0.	γ. Calc.
1. Anthracene in benzene.		(for $I_0 = 290$.)	(for $\kappa = 60$.)
0·1	28	—	~1
1·0	260	—	0·99
5	270	—	0·97
10	280	0·96	0·94
20	260	0·89	0·87
40	240	0·83	0·81
60	210	0·72	0·74
80	190	0·66	0·68
100	180	0·64	0·63
200	130	0·45	0·45
300	95	0·32	0·36
400	75	0·25	0·29
500	60	0·21	0·25
2. Anthracene in hexane.		(for $I_0 = 280$.)	(for $\kappa = 100$.)
0·1	19	—	~1·0
1	212	—	0·99
5	237	—	0·95
10	250	0·89	0·91
20	230	0·82	0·83
40	200	0·71	0·71
60	170	0·61	0·63
80	150	0·54	0·56
100	140	0·50	0·50
3. Anthracene in ethanol.		(for $I_0 = 280$.)	(for $\kappa = 100$.)
0·1	17	—	~1·0
1	175	—	0·99
5	220	—	0·95
10	250	0·90	0·91
20	230	0·82	0·83
40	200	0·71	0·71
60	177	0·63	0·63
80	158	0·56	0·56
100	145	0·52	0·50
7. 3 : 4-Benzpyrene in benzene.		(for $I_0 = 230$.)	(for $\kappa = 77$.)
0·1	36	—	~1·0
1	174	—	~1·0
5	225	0·97	0·96
10	214	0·93	0·93
20	195	0·85	0·87
40	170	0·74	0·77
60	150	0·65	0·69
80	140	0·61	0·62
100	124	0·54	0·56
200	86	0·37	0·39
300	66	0·27	0·30
500	45	0·20	0·21

$c \times 10^4$ (mol./l.).	I.*	γ. Obs. I/I_0.	γ. Calc.
4. 1 : 2-Benzanthracene in benzene.		(for $I_0 = 300$.)	(for $\kappa = 40$.)
0·1	34	—	~1·0
1	206	—	~1·0
5	291	0·97	0·98
10	281	0·94	0·96
20	281	0·94	0·93
40	259	0·86	0·86
60	250	0·83	0·81
80	236	0·78	0·76
100	220	0·73	0·72
200	178	0·59	0·56
300	140	0·47	0·45
500	110	0·36	0·33
5. 9 : 10-Dimethyl-1 : 2-benzanthracene in benzene.		(for $I_0 = 220$.)	(for $\kappa = 83$.)
0·1	38	—	~1·0
1	205	—	0·99
5	212	0·96	0·96
10	212	0·96	0·92
20	175	0·83	0·85
40	155	0·74	0·75
60	142	0·68	0·67
80	133	0·63	0·60
100	125	0·59	0·54
200	94	0·41	0·38
300	72	0·31	0·28
500	50	0·22	0·19
6. 20-Methylcholanthrene in benzene.		(for $I_0 = 280$.)	(for $\kappa = 77$.)
0·1	37	—	~1·0
0·3	112	—	~1·0
1	220	—	~1·0
2·5	275	0·98	0·98
5	270	0·97	0·96
10	256	0·92	0·93
25	227	0·81	0·84
50	200	0·71	0·72
100	155	0·55	0·56
8. Ethylchlorophyllide in ethanol.		(for $I_0 = 700$.)	(for $\kappa = 2 \times 10^5$.)
0·01	35	—	0·89
0·05	115	—	0·50
0·075	135	—	0·40
0·1	150 (230) †	0·33 †	0·33
0·2	150	0·21	0·20
0·4	80	0·14	0·11
0·6	50	0·07	0·07
0·8	35	0·05	0·05
1·0	25	0·04	0·04

* In arbitrary units. Expts. 1—5 were carried out under identical conditions and the units are recorded on the same scale. The units of experiments 6, 7, and 8 are not comparable either amongst each other or with those of expts. 1—5.

† Extrapolated.

TABLE II.

Self-quenching constants of various fluorescent substances.

Substance.	Solvent.	Quenching constant, κ.	Substance.	Solvent.	Quenching constant, κ.
Ethylchlorophyllide	Ethanol	2×10^5	3 : 4-Benzpyrene	Benzene	77
Anthracene	Benzene	60	9 : 10-Dimethyl-1 : 2-benzanthracene	Benzene	83
Anthracene	Hexane	100	1 : 2-Benzanthracene	Benzene	40
Anthracene	Ethanol	100	Pyrene	Benzene	<10
20-Methylcholanthrene	Benzene	77	1 : 2 : 5 : 6-Dibenzanthracene	Benzene	<10

The rate of photochemical formation of dianthracene (D) from anthracene (An) is given from equations (1), (2), and (3*a*) for the stationary state {$[An^*] = I_{abs.}/(\bar{k}_2 + \bar{k}_{3a}[An])$ and the barred constants now refer to anthracene in particular}

$$d[D]/dt = k_{3a}[An^*][An] = I_{abs.}[An]/\{(\bar{k}_2/\bar{k}_{3a}) + [An]\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

This equation is identical with that found by Bodenstein (*Z. physikal. Chem.*, 1914, **87**, 93) to represent all the experiments of Luther and Weigert (*ibid.*, 1905, **51**, 297; **53**, 385) and of Weigert and Krüger (*ibid.*, 1913, **85**, 579; 1914, **86**, 383). The value of 10 for $\bar{k}_2/\bar{k}_{3a}$ given by Bodenstein (*loc. cit.*, p. 97) refers to anthracene in toluene at 105°, concentrations being expressed in millimols./l. The corresponding quenching constant (in mols./l.) is given by $\kappa_{An} = \bar{k}_{3a}/\bar{k}_2 = 10^{-1} \times 10^3 = 10^2$ which is in good agreement with the value for anthracene derived from quenching experiments (Table II) and also with that derived from the experiments of Bowen and Williams (*loc. cit.*, Table III) and Pringsheim (*loc. cit.*).

In photosensitised oxidations, equations corresponding to an interaction between the excited and the non-excited dye have been used by several authors (cf. Gaffron, *Biochem. Z.*, 1933, **264**, 251; Koblitz and Schuhmacher, *Z. physikal. Chem.*, 1937, *B*, **35**, 11; Bowen and Williams, *loc. cit.*). These were found necessary in order to account for the kinetics of the reaction, although their full significance and their connection with self-quenching has often not been recognised.

A particularly interesting case is afforded by the behaviour of chlorophyll or ethylchlorophyllide. From the fact that in ordinary dilute solutions (10^{-3}—10^{-4} mol./l.) the fluorescence efficiency is very low and not very strongly influenced by either oxygen or reducing agents, it has been concluded that the process determining the lifetime of the excited chlorophyll molecule must be a special one. Franck and Livingston (*J. Chem. Physics*, 1941, **9**, 184) suggested that this was due to a change of the excited chlorophyll molecule into a reactive tautomer. Although this may be possible, it is not essential to explain the striking behaviour of chlorophyll, which can be accounted for quantitatively by its very strong self-quenching effect (Table II). One can easily see that the strong interaction between excited and non-excited chlorophyll molecules determines the lifetime of the excited state. The reaction is given by

$$Chl^* + Chl \longrightarrow 2Chl \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

Fluorescence emission, even in solutions of 10^{-3} M, is practically suppressed. In the presence of an acceptor molecule (Acc) a number of the excited chlorophyll molecules will interact according to the general quenching reaction :

$$Chl^* + Acc \longrightarrow Chl^+ + Acc^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

which is the primary process and rate-determining step for the subsequent photosensitised oxidation (Weiss, *Trans. Faraday Soc.*, 1938, **34**, 451; 1939, **35**, 48; Carter and Weiss, *Proc. Roy. Soc.*, 1940, *A*, **174**, 351). In this case the stationary concentration of Chl^* is given by

$$[Chl^*] = I_{abs.}/(k_{14}[Chl] + k_{15}[Acc]) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (16)$$

and for the rate of the photosensitised oxidation, which is identical with the rate of reaction (15), we have

$$-d[Acc]/dt = k_{15}[Chl^*][Acc] = k_{15}I_{abs.}[Acc]/(k_{14}[Chl] + k_{15}[Acc]) \quad . \quad . \quad . \quad . \quad (17)$$

For the quantum efficiency of the photo-oxidation :

$$\gamma_{ox.} = -\frac{d[Acc]}{dt}\left(\frac{1}{I_{abs.}}\right) = \frac{(k_{15}/k_{14})[Acc]/[Chl]}{(k_{15}/k_{14})[Acc]/[Chl] + 1} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (18)$$

This is identical with the empirical equation given by Gaffron (*Ber.*, 1927, **60**, 755) to represent all his results for the acceptor thiosinamine with ethylchlorophyllide as sensitiser in acetone solutions. In this particular case he found $K = (k_{15}/k_{14}) = 0{\cdot}2$, which means that the self-quenching interaction between the ethylchlorophyllide molecules is still 5 times faster than the interaction (15) with the acceptor molecules.

Experimental.

Fluorescence Measurements.—The apparatus used was the direct-reading, one-cell fluorimeter already described (Weil-Malherbe, J., 1943, 303; *Biochem. J.*, 1944, in the press), but modifications in its use were made : the photo-cell ("EEL" selenium barrier layer cell of 45 mm. diameter) was placed in line with the incident beam of filtered ultra-violet light. Such an arrangement is preferable when working with concentrations where the incident light is absorbed in a small depth. The beam of fluorescent light was filtered through a layer of 5% sodium nitrite solution in order to eliminate any scattered ultra-violet radiation, and through a suitable colour filter. Sensitivity of galvanometer deflection was controlled by inserting shutters of various aperture between light source and solution.

All measurements were carried out in purified nitrogen. The gas stream was saturated with the solvent used by passage through a wash-bottle before entering the solution. A zero reading with pure solvent was taken after every reading, and all figures have been corrected accordingly.

Grateful acknowledgment is made of the generous gift by Prof. J. W. Cook, F.R.S., of several hydrocarbons used in this investigation.

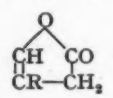
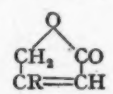
King's College, University of Durham, and Cancer Research Laboratory,
Royal Victoria Infirmary, Newcastle-upon-Tyne. [*Received, May 6th*, 1944.]

152. *The Synthesis of Some Unsaturated γ-Lactones.*

By G. Swain, A. R. Todd, and W. S. Waring.

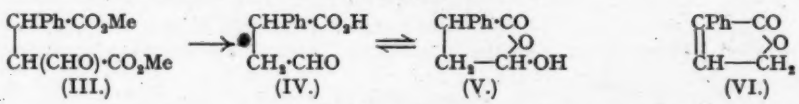
With a view to gain insight into the structural features essential to the physiological activity of the cardiac glycosides, a number of unsaturated γ-lactones bearing simple cyclic substituents in the α-, β-, or γ-positions have been prepared. In the case of the α- and β-substituted compounds all those obtained were $\Delta^{\alpha\beta}$-butenolides, although their mode of preparation from substituted β-formylpropionic acids might have been expected to give $\Delta^{\beta\gamma}$-butenolides. In the γ-substituted series $\Delta^{\beta\gamma}$-butenolides were readily obtained by lactonising γ-keto-acids. A number of the lactones prepared have been examined for digitalis-like action. None of those examined showed any activity in cats although some caused systolic arrest of the frog heart. This is in accord with the published findings of other investigators working on similar lines.

Although it is known that the unsaturated γ-lactone grouping in the steroid aglycones of the cardiac glycosides plays a dominant part in determining the physiological activity of the natural drugs, the mechanism of their action on the heart is unknown. At the time when the investigations now described were commenced (1939) no evidence was available as to the part, if any, played by the steroid nucleus in the action of these substances. It seemed therefore of interest to attempt the synthesis of compounds containing a similar unsaturated lactone grouping attached to simpler ring systems in the hope of obtaining information on this point and, perhaps, of preparing comparatively simple substances with cardiotonic properties similar to those of the natural drugs. When much of the work described in this paper had been carried out, several publications dealing with similar synthetic studies appeared (Elderfield *et al.*, *J. Org. Chem.*, 1941, **6**, 261, 270, 273, 289; 1942, **7**, 374, 444), together with others describing analogous work in the steroid series (Ruzicka, Reichstein, and Fürst, *Helv. Chim. Acta*, 1941, **24**, 76; Elderfield *et al.*, *J. Org. Chem.*, 1942, **7**, 362, 383). Circumstances have delayed for some time the completion and publication of our studies. We now wish to record our results; although in two cases the same compounds have been prepared by Elderfield and his collaborators, we have, in general, employed different synthetic methods. Until 1941, the accepted structure of the cardiac aglycones of the *Digitalis–Strophanthus* group, put forward largely on the basis of the investigations of Jacobs and of Tschesche, was represented by (I), where R is a steroid nucleus variably substituted. According to this view, they were β-substituted $\Delta^{\beta\gamma}$-butenolides and it was to the synthesis of such compounds and of corresponding α- and γ-substituted lactones that we first directed our attention. During the course of our work a re-examination of the natural aglycones by Paist, Blout, Uhle, and Elderfield (*J. Org. Chem.*, 1941, **6**, 273) has shown that structure (I) is erroneous and that they are in fact β-substituted $\Delta^{\alpha\beta}$-butenolides (II).

(I.)   (II.)

All our attempts to obtain α- or β-substituted $\Delta^{\beta\gamma}$-butenolides by lactonising the corresponding α- or β-substituted β-formylpropionic acids failed; in every case migration of the double bond occurred and the products were $\Delta^{\alpha\beta}$-butenolides. The preparation of γ-substituted $\Delta^{\beta\gamma}$-butenolides, on the other hand, was readily effected by lactonising the appropriate γ-keto-acids.

(a) *α-Substituted Lactones.*—In our first experiments we endeavoured to prepare α-phenyl-$\Delta^{\beta\gamma}$-butenolide by the following route. Methyl phenylsuccinate was formylated readily by ethyl formate and sodium, but the product gave analytical values suggesting that it was a mixture of methyl β-formyl-α-phenylsuccinate (III) with the corresponding diethyl or methyl ethyl esters formed by ester interchange during formylation; in accordance with this view hydrolysis, which was accompanied by decarboxylation, gave *β-formyl-α-phenylpropionic acid* (IV), characterised as its 2 : 4-*dinitrophenylhydrazone*.


(III.) (IV.) (V.) (VI.)

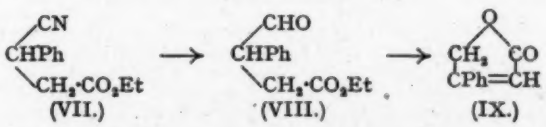
The acid (IV) distilled as a thick liquid which, on standing, set to a sticky solid; it was insoluble in cold sodium carbonate solution but dissolved slowly in sodium hydroxide. In view of this, and of the facts that it did not reduce Tollens's reagent and gave only a faint colour in the Legal test (alkaline sodium nitroprusside), it seems probable that the acid exists mainly in the form of the isomeric hydroxy-lactone (V). Several unsuccessful attempts were made to dehydrate the aldehydo-acid (IV) by means of acetic anhydride, piperidine, dimethylaniline and triethanolamine. Eventually, lactonisation was achieved by using hydrobromic acid in acetic acid, although the yield of lactone was low and much phenylsuccinic acid was formed. The lactone reduced Tollens's reagent and gave a positive Legal test, but its absorption spectrum showed a maximum at 2565 A. ($\varepsilon = 9820$), indicating that the double bond in the lactone ring was conjugated with the aromatic nucleus; it is therefore to be regarded as *α-phenyl-$\Delta^{\alpha\beta}$-butenolide* (VI). No trace of the $\Delta^{\beta\gamma}$-isomer was obtained. The possibility that the initial formylation of methyl phenylsuccinate might have led to methyl α-formyl-α-phenylsuccinate rather than (III), and that the final product of the synthesis might accordingly have been β-phenyl-$\Delta^{\alpha\beta}$-butenolide (IX), was ruled out by the synthesis of (IX) by an unambiguous route (see below). The lactone (VI) was also obtained by heating *methyl γγ-dimethoxy-α-phenylbutyrate* with hydrobromic acid in

acetic acid, but the yield was no greater than with the free aldehydo-acid. During attempts to dehydrate (IV) with acetic anhydride, a saturated lactone was obtained, which, on the basis of its analysis and properties, we regard as *γ-acetoxy-α-phenylbutyrolactone* formed by acetylation of the isomeric form (V) of the aldehydo-acid.

Since the physiological activity of the cardiac aglycones is enhanced and, in some therapeutically important respects, modified by glycosidic combination with sugars in the natural drugs, it was desirable that efforts be made to obtain a lactone analogous to (VI) containing a hydroxyl group which might serve as a point of attachment for a sugar residue. To this end we endeavoured to apply the method described above, starting with 4-hydroxyphenylsuccinic acid, which was prepared in good yield from ethyl α-cyano-4-acetoxycinnamate by addition of hydrogen cyanide and subsequent hydrolysis of the crude ethyl αβ-dicyano-β-(4-acetoxyphenyl)-propionate. Attempted formylation of *methyl 4-acetoxyphenylsuccinate* gave only syrupy, unidentifiable products. Methyl 4-methoxyphenylsuccinate, however, was formylated smoothly by ethyl formate and sodium, yielding a mixture of methyl and ethyl β-formyl-α-(4-methoxyphenyl)succinates which, on hydrolysis, gave a product whose behaviour indicated it to be a mixture of the expected aldehydo-acid and the tautomeric hydroxy-lactone analogous to (IV) and (V). For purposes of characteristisation, the 2 : 4-*dinitrophenylhydrazone* of the acid was prepared but the main bulk of material was not further purified and was heated directly with hydrobromic acid in acetic acid in the hope that simultaneous lactonisation and demethylation might occur. The product was, however, α-(4-*methoxyphenyl*)-$\Delta^{\alpha\beta}$-*butenolide* and we were unable to effect demethylation under conditions which did not simultaneously disrupt the lactone ring.

Stobbe (*J. pr. Chem.*, 1914, **89**, 329) prepared a mixture of ethyl Δ^1-*cyclo*pentenylsuccinate and ethyl *cyclo*pentylidenesuccinate by condensing *cyclo*pentanone with ethyl succinate in presence of sodium ethoxide; a similar condensation using *cyclo*hexanone followed by hydrolysis gave Δ^1-cyclo*hexenylsuccinic acid*, which was readily hydrogenated to *cyclo*hexylsuccinic acid. *Methyl* cyclo*hexylsuccinate* reacted with ethyl formate in presence of sodium to give, by analogy with the corresponding case of the phenylsuccinate, a mixture of methyl and ethyl esters of β-formyl-α-*cyclo*hexylsuccinic acid which on hydrolysis and decarboxylation yielded *β-formyl-α-cyclohexylpropionic acid*. This acid reduced Tollens's reagent only on warming, and on being heated with hydrobromic acid in acetic acid it gave α-cyclo*hexyl*-$\Delta^{\alpha\beta}$-*butenolide* as a colourless mobile liquid which reduced Tollens's reagent in the cold and gave a positive Legal reaction.

(b) *β-Substituted Lactones.*—In the first instance it was decided to attempt the synthesis of β-phenyl-$\Delta^{\beta\gamma}$-butenolide (I; R = Ph) by the action of hydrobromic acid and acetic acid on *ethyl β-formyl-β-phenylpropionate* (VIII), prepared by reduction of ethyl β-phenyl-β-cyanopropionate (VII) by Stephen's method. Torrey, Kuck, and Elderfield (*J. Org. Chem.*, 1941, **6**, 289) have, since this preparation was carried out, reported the synthesis of (VIII) by this method to be impracticable, but although the yield in the reduction is not high,



the starting material is readily accessible and no serious difficulties were encountered by us. The ester (VIII) was characterised as its 2 : 4-dinitrophenylhydrazone, m. p. 129—130°. Torrey, Kuck, and Elderfield (*loc. cit.*) prepared this derivative from a specimen of aldehydo-ester obtained by hydrogenation of impure ethyl β-formyl-β-phenylpropenoate, and record m. p. 108·5—109°. It is difficult to understand this discrepancy in m. p. unless it be due to dimorphism, although we found no evidence for the existence of two forms. Treatment of (VIII) with hydrobromic acid in acetic acid gave β-phenyl-$\Delta^{\alpha\beta}$-butenolide (IX); that the double bond occupied the αβ- and not the βγ-position followed from the presence in the absorption spectrum of a maximum of high intensity at 2730 A. (ε = 20,500). This is in accord with the results of Elderfield and his co-workers, who have also prepared (IX) by a different route (Rubin, Paist, and Elderfield, *J. Org. Chem.*, 1941, **6**, 261), and also failed to obtain the corresponding $\Delta^{\beta\gamma}$-butenolide.

Attempts to extend the method used for the synthesis of (IX) to β-(4-hydroxyphenyl)-$\Delta^{\alpha\beta}$-butenolide met with little success. *Ethyl 4-acetoxybenzylidenemalonate* reacted readily with potassium cyanide to give *ethyl β-cyano-β-(4-acetoxyphenyl)propionate*, although some hydrolysis of the acetoxy-group occurred during the reaction, and the product had to be reacetylated before it could be crystallised. No trace of aldehyde was obtained when efforts were made to reduce the cyano-ester by Stephen's method. It was hoped that *ethyl β-cyano-β-(4-methoxyphenyl)propionate*, prepared in similar fashion from ethyl anisylidenemalonate, might be reduced more readily, but only traces of aldehyde were obtained. In view of these results this method of approach was not further pursued. A specimen of β-(4-methoxyphenyl)-$\Delta^{\alpha\beta}$-butenolide was, however, prepared by carrying out a Reformatsky reaction with ω-acetoxy-4-methoxyacetophenone and ethyl bromoacetate and treating the product with hydrobromic acid. This method is analogous to that used by Linville and Elderfield (*J. Org. Chem.*, 1941, **6**, 270) for the preparation of β-phenyl-$\Delta^{\alpha\beta}$-butenolide, and indeed the synthesis of β-(4-methoxyphenyl)-$\Delta^{\alpha\beta}$-butenolide by a similar method was subsequently described by Marshall, Kuck, and Elderfield (*J. Org. Chem.*, 1942, **7**, 444).

(c) *γ-Substituted Lactones.*—In order to have available a range of unsaturated lactones varying in the nature and position of substituents, several γ-substituted $\Delta^{\beta\gamma}$-butenolides were prepared. On heating

β-(4-*hydroxybenzoyl*)*propionic acid* with acetic anhydride, a product was obtained which, purified by sublimation in a vacuum, had the properties expected of γ-(4-*acetoxyphenyl*)-$\Delta^{\beta\gamma}$-*butenolide*. Lactonisation of β-(4-methoxyphenyl)propionic acid in the same manner gave γ-(4-*methoxyphenyl*)-$\Delta^{\beta\gamma}$-*butenolide*.

In the naphthalene series γ-(2-*acetoxy*-6-*naphthyl*)-$\Delta^{\beta\gamma}$-*butenolide* was obtained by heating β-(2-hydroxy-6-naphthoyl)propionic acid with acetic anhydride. For the preparation of this acid, 2-ethoxynaphthalene—a supply of which happened to be available—was condensed with succinic anhydride by means of aluminium chloride in nitrobenzene. In addition to β-(2-hydroxy-6-naphthoyl)propionic acid, β-(2-*ethoxy*-6-*naphthoyl*)-*propionic acid* and β-(2-*ethoxy*-1-*naphthoyl*)*propionic acid* were isolated from the reaction. Although β-(2-ethoxy-6-naphthoyl)propionic acid could be readily de-ethylated, β-(2-ethoxy-1-naphthoyl)propionic acid when heated with hydrobromic acid in acetic acid gave only β-naphthol. Exactly similar behaviour in this and other respects was shown by β-(2-methoxy-1-naphthoyl)propionic acid (Short, Stromberg, and Wiles, J., 1936, 320), a sample of which was kindly supplied by Dr. W. F. Short for comparison.

Several of the lactones described in this paper as well as aconic acid (β-carboxy-$\Delta^{\beta\gamma}$-butenolide) were examined pharmacologically for digitalis-like action. These tests were carried out by Dr. J. Raventos in the Biological Department of Messrs. Imperial Chemical Industries Ltd., Blackley, and to him we are greatly indebted.

The following lactones were tested on cats by intravenous injection, the auricular and ventrical contractions being simultaneously recorded: α-phenyl-$\Delta^{\alpha\beta}$-butenolide (30 mg./kg.), β-phenyl-$\Delta^{\alpha\beta}$-butenolide (15 mg./kg.), γ-phenyl-$\Delta^{\beta\gamma}$-butenolide (100 mg./kg.), γ-(2-acetoxy-6-naphthyl)-$\Delta^{\beta\gamma}$-butenolide (25 mg./kg.), aconic acid (20 mg./kg.). None of them showed any digitalis-like interference with the conduction of impulses. On the other hand, when tested on the isolated frog heart by perfusion in Ringer solution by the inferior *venæ cavæ*, α-*cyclo*hexyl-$\Delta^{\alpha\beta}$-butenolide caused systolic arrest after 5 mins. at a dilution of 1 in 2000; slight action could be detected at a dilution of 1 in 10,000. α-Phenyl-$\Delta^{\alpha\beta}$-butenolide, γ-(4-acetoxyphenyl)-$\Delta^{\beta\gamma}$-butenolide, and aconic acid were virtually devoid of activity in the frog test.

More extended pharmacological examination was not made as the above results appeared to be rather similar to those recorded by other workers who have examined a considerable range of synthetic unsaturated lactones (Chen, Steldt, Fried, and Elderfield, *J. Pharm. Exp. Ther.*, 1942, **74**, 381; Chen and Elderfield, *ibid.*, 1942, **76**, 81; Krayer, Mendez, Espanés, and Linstead, *ibid.*, 1942, **74**, 372). From their results and our own it would seem that, although quite a number of synthetic non-steroid unsaturated lactones, including such simple compounds as methyl coumalate, may cause systolic arrest of the frog heart, none so far prepared shows the characteristic action of the cardiac glycosides or agylcones on the mammalian heart. It is doubtful whether in this case the frog test is of any value in assessing digitalis-like activity of synthetic compounds.

Experimental.

Formylation of Methyl Phenylsuccinate.—Methyl phenylsuccinate (33 g.; Anschütz, *Annalen*, 1907, **354**, 128) was dissolved in dry ether (150 c.c.), and ethyl formate (16·8 g.) and sodium wire (4·0 g.) added. The flask was closed by a calcium chloride tube and set aside at room temperature. Little visible reaction occurred at first but after 3 days all the sodium had disappeared and a brown resin had separated which dissolved on addition of water (250 c.c.). The ethereal layer was discarded, and the aqueous layer acidified and extracted with ether. The extract was washed, dried, evaporated, and the thick oily residue distilled under reduced pressure. The formylation product was obtained as a colourless syrupy liquid (16 g.), b. p. 130—135°/0·3 mm. (bath temp. 160—170°) [Found: C, 63·2; H, 6·1. $C_9H_8O(CO_2Me)_2$ requires C, 62·4; H, 5·6%].

β-Formyl-α-phenylpropionic Acid.—The above product (15·0 g.), dissolved in glacial acetic acid (50 c.c.), was refluxed for 3 hours with hydrochloric acid (50 c.c., *d* 1·16). The cooled solution was partly neutralised with sodium hydroxide (20 g. in 300 c.c. of water), saturated with salt, and extracted with ether. The ethereal solution was washed several times with aqueous sodium carbonate (10%), the combined washings acidified with hydrochloric acid, and the oil which separated taken up in ether and dried over sodium sulphate. The syrupy residue (10·0 g.) left after removal of the ether was distilled under reduced pressure. *β-Formyl-α-phenylpropionic acid* (5·7 g.) was obtained as a viscous, colourless syrup, b. p. 137—142°/0·02 mm. (bath temp. 175—180°) in which some solid separated on prolonged standing. A redistilled specimen set slowly to a sticky solid, m. p. 49—51° (Found: C, 67·1; H, 5·9. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·6%). The distilled product was insoluble in cold sodium carbonate solution, dissolved slowly in cold sodium hydroxide, did not reduce Tollens's reagent, and gave only an extremely weak, transient maroon in the Legal test. (Light absorption in alcohol: max. at 2580 A., $\varepsilon = 194$.) The acid gave a 2 : 4-*dinitrophenylhydrazone*, which crystallised from acetic acid in orange prisms, m. p. 216—218° (decomp.) (Found: C, 53·4; H, 4·0; N, 15·1. $C_{16}H_{14}O_6N_4$ requires C, 53·6; H, 3·9; N, 15·6%). The 2 : 4-dinitrophenylhydrazone has the curious property of crystallising either in yellow prisms or in mixtures of yellow and orange prisms; both forms have the same m. p.

γ-Acetoxy-α-phenylbutyrolactone.—β-Formyl-α-phenylpropionic acid (2·0 g.) was refluxed for 20 hours with acetic anhydride (7 c.c.). Excess of anhydride was decomposed with water, and the product extracted with ether. The orange oil (1·5 g.) left after removal of ether distilled at 160—170° (bath temp.)/0·01—0·02 mm. as a pale greenish-yellow syrup, which solidified on standing and was then recrystallised from aqueous methanol. *γ-Acetoxy-α-phenylbutyrolactone* separated in colourless prismatic plates, m. p. 84—85° (Found: C, 65·2; H, 5·5. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%). The purified lactone did not reduce Tollens's reagent and gave no colour in the Legal test. The crude distillate, however, partly reduced Tollens's reagent and showed an intense violet changing through maroon to orange-brown in the Legal reaction.

α-Phenyl-$\Delta^{\alpha\beta}$-butenolide.—β-Formyl-α-phenylpropionic acid (10 g.), dissolved in acetic acid (20 c.c.), was heated under reflux for 4 hours with a solution of hydrobromic acid in acetic acid (50 g. saturated at 0°). The product was poured into water, extracted with ether, and the extract thoroughly washed, dried over sodium sulphate, and evaporated. The brown oily residue (3·7 g.) was distilled under a pressure of 5×10^{-3} mm. (bath temp. 120—130°). The colourless distillate (1·8 g.) solidified, and then crystallised from benzene–light petroleum (1 : 1) in colourless plates (1·4 g.), m. p. 89° (Found: C, 75·1; H, 5·1. $C_{10}H_8O_2$ requires C, 75·0; H, 5·0%). The *lactone* reduced Tollens's reagent almost immediately and showed an intense violet rapidly changing through maroon to orange-brown in the Legal test. (Light

absorption in alcohol: max. 2565 A., ε = 9820.) The sodium carbonate washings on acidification yielded an oil (1·6 g.) from which phenylsuccinic acid was isolated.

Methyl γγ-Dimethoxy-α-phenylbutyrate.—β-Formyl-α-phenylpropionic acid (3·0 g.), dissolved in dry methanolic hydrogen chloride (16 c.c. of 1%), was allowed to stand for 12 hours at room temperature, then refluxed for 15 minutes and set aside for a further 48 hours. The product was poured into potassium carbonate solution (100 c.c. of 5%), and the oil which separated taken up in ether. The residue (3·3 g.) left after removal of the ether was distilled under reduced pressure. *Methyl γγ-dimethoxy-α-phenylbutyrate* (2·9 g.) was obtained as a colourless oil, b. p. 114—115°/0·1—0·2 mm. (Found: C, 65·8; H, 7·5. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·6%). It gave an intense violet rapidly changing to yellow in the Legal test and reduced Tollens's reagent rapidly at room temperature. *Action of hydrobromic acid in acetic acid.* The ester (3 g.) was refluxed for 4 hours with a solution of hydrobromic acid in acetic acid (15 c.c. of 33%). The product was poured into water, extracted with ether, and washed with sodium carbonate solution (5%). The neutral fraction (0·3 g.) recovered from the ether was distilled at 75°/10^{-4} mm., and the crystalline distillate (0·1 g.) recrystallised from benzene–light petroleum (1 : 1). α-Phenyl-$\Delta^{\alpha\beta}$-butenolide was obtained in colourless plates, m. p. 89°, undepressed in admixture with the specimen already described.

Methyl 4-Hydroxyphenylsuccinate.—4-Hydroxyphenylsuccinic acid (138 g.; Chrzaszczewska, *Chem. Zentr.*, 1926, **97**, 2, 2906) was esterified by refluxing for 2½ hours with methanolic hydrogen chloride (1100 c.c. of 4%). The *ester*, worked up in the usual manner and recrystallised from benzene–light petroleum (3 : 1), formed colourless prisms, m. p. 76—77°. Dave and Nargund (*J. Univ. Bombay*, 1938, **7**, 196), give b. p. 150—160°/0·20 mm. (Found: C, 60·9; H, 5·8. Calc. for $C_{13}H_{14}O_5$: C, 60·5; H, 5·9%). Acetylation of the ester by refluxing with acetic anhydride for 2 hours gave *methyl 4-acetoxyphenylsuccinate*, which crystallised from aqueous alcohol in colourless needles, m. p. 55° (Found: C, 60·0; H, 5·8. $C_{14}H_{16}O_6$ requires C, 60·0; H, 5·7%). Attempts to condense this product with ethyl formate and sodium failed.

4-Methoxyphenylsuccinic Acid.—To methyl 4-hydroxyphenylsuccinate (2·8 g.) dissolved in 10% sodium hydroxide solution methyl sulphate (3 c.c.) was added, and the mixture heated on a steam-bath for 1 hour with frequent shaking. More methyl sulphate (3 c.c.) was added together with more sodium hydroxide, and heating continued for another hour. Acidification of the hot solution caused the separation of a crystalline precipitate of 4-methoxyphenylsuccinic acid (1·9 g.). This was filtered off, and after two crystallisations from hot water, had m. p. 201° (Found: C, 59·0; H, 5·5; MeO, 13·3; equiv., 112. Calc. for $C_{11}H_{12}O_5$: C, 58·9; H, 5·4; 1MeO, 13·8%; equiv., 112). This acid has been described by various workers, who record m. p.'s ranging from 191° (Chrzaszczewska, *loc. cit.*) to 207—208° (Corson and Stoughton, *J. Amer. Chem. Soc.*, 1928, **50**, 2825).

Methyl 4-Methoxyphenylsuccinate.—Methyl 4-hydroxyphenylsuccinate (11·9 g.) and methyl iodide (7·1 g.) were dissolved in acetone and refluxed with anhydrous potassium carbonate for 2½ hours. More methyl idodide (7·1 g.) was added, and refluxing continued for 4½ hours longer. Water was then added, and the precipitated oil taken up in ether. The ethereal solution was washed with alkali, then water, and dried over sodium sulphate. Removal of the solvent left an oil (10·7 g.), which distilled completely between 130—135°/10^{-3} mm. as a colourless liquid (Found: C, 62·0; H, 6·6. Calc. for $C_{13}H_{16}O_5$: C, 61·9; H, 6·4%). Corson and Stoughton (*loc. cit.*), who prepared this ester by a different route, describe it as a solid, m. p. 93—94°, for which they could get no consistent analytical figures.

α-(4-Methoxyphenyl)-$\Delta^{\alpha\beta}$-butenolide.—Methyl 4-methoxyphenylsuccinate (20 g.) and ethyl formate (12 g.) were dissolved in dry ether (200 c.c.) and allowed to react with sodium wire at room temperature for 3 days. Water was added to dissolve the resinous product, and the alkaline solution separated. Acidification and extraction with ether yielded a viscous red oil (11·4 g.), which distilled as a thick, clear yellow liquid at 165°/5 × 10^{-2} mm. This product was evidently a mixture of the methyl and the ethyl ester [Found: C, 62·3; H, 6·2. Calc. for $C_{10}H_{10}O_3(CO_2Me)_2$: C, 60·0; H, 5·7%].

The formylation product (7·8 g.) was refluxed with a mixture of glacial acetic acid (25 c.c.) and concentrated hydrochloric acid (20 c.c.) for 3½ hours. The reaction mixture was partly neutralised with sodium hydroxide, extracted with ether, and the extract washed several times with dilute sodium cabonate solution. The carbonate washings were acidified, the precipitated oil taken up in ether, and the solution washed, dried, and evaporated. A dark oil was left (4·6 g.), which distilled at 180°/2 × 10^{-3} mm. as a thick orange-coloured liquid. It neither reduced Tollens's reagent nor gave a colour with ferric chloride, but a weak brown colour developed in the Legal reaction. From this behaviour, and evidence of a lacto-group during titration, it would seem that the aldehydo-acid exists largely in the form of the isomeric hydroxylactone. The crude acid was converted without further purification into the unsaturated lactone. Treatment of the oil with 2 : 4-dinitrophenylhydrazine in the usual way gave *β-formyl-α-(4-methoxyphenyl)propionic acid 2 : 4-dinitrophenylhydrazone*, m. p. 156—157° (Found: N, 14·8. $C_{17}H_{16}O_7N_4$ requires N, 14·4%).

The crude aldehydo-acid (2 g.) was refluxed with a mixture of glacial acetic acid (7 c.c.) and a solution of hydrobromic acid in acetic acid (20 c.c. of 50%) for 4 hours. Water was then added, and the mixture extracted with ether. The ethereal solution, after being washed with water and sodium bicarbonate solution, was finally dried over sodium sulphate, and the solvent removed. An oil (400 mg.) was left which partly crystallised on standing for several days. It was purified by dissolving it in ether and shaking the solution with very dilute sodium hydroxide to remove traces of phenols. After removal of the solvent, the residue was sublimed in a molecular still. The crystalline sublimate, which was not very soluble in ether, crystallised from benzene containing a little light petroleum in colourless plates, m. p. 123—124°. It reduced Tollens's reagent in the cold, and gave a positive Legal reaction (Found: C, 69·4; H, 5·3. $C_{11}H_{10}O_3$ requires C, 69·5; H, 5·3%). Light absorption in alcohol: max. 2790 A. (ε, 14,000).

Δ^1-cyclo*Hexenylsuccinic Acid.*—Alcohol-free sodium ethoxide, prepared from molecular sodium (23 g.) and dry alcohol (46 g.) in benzene, was cooled in an ice–salt mixture, *cyclo*hexanone (84 g.) and succinic ester (87 g.) added, and the reaction mixture diluted with dry ether (50 c.c.). The reaction vessel was kept in an ice-box for 3 days, after which the reaction was allowed to proceed at room temperature. At the end of two weeks, water was added to the mixture. The solid dissolved, and the aqueous layer was separated and almost neutralised with sulphuric acid. The weakly alkaline solution, after being repeatedly extracted with ether to remove succinylsuccinic ester (14 g.), was made strongly acid with sulphuric acid, which precipitated a heavy brown oil (132 g.). This was separated, and heated with continuous stirring for 45 mins. with excess of barium hydroxide solution, the temperature being maintained just below the b. p. The insoluble barium salt was collected, decomposed with hot dilute hydrochloric acid, and the oily acid taken up in ether, the solution dried over sodium sulphate, and the solvent removed. The oily residue (75 g.) was triturated with cold xylene, the crude *acid* being left as a white powder (36 g.). Recrystallisation from hot water (charcoal) gave colourless prisms (35 g.), m. p. 146—147° (Found: C, 60·4; H, 7·3; equiv., 100. $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1%; equiv., 99). *cyclo*Hexylidenesuccinic acid has m. p. 175° (Ingold, Seeley, and Thorpe, J., 1923, **123**, 853), and unlike our product gives *cyclo*hexanone on oxidation with permanganate.

cyclo*Hexylsuccinic Acid.*—*cyclo*Hexenylsuccinic acid (35 g.), hydrogenated in methano solution by means of a platinum oxide catalyst, absorbed 4 l. of hydrogen (Calc. for 1 double bond: 3·9 l.). Removal of methanol and recrystallisation from hot water gave *cyclo*hexylsuccinic acid as colourless plates, m. p. 146—147° (depressed on admixture with *cyclo*hexenylsuccinic acid) (Found: C, 59·6; H, 8·2. Calc. for $C_{10}H_{16}O_4$: C, 60·0; H, 8·0%). Naps and Johns (*J. Amer Chem. Soc.*, 1940, **62**, 2450) give m. p. 146°.

Methyl cyclo*Hexylsuccinate.*—*cyclo*Hexylsuccinic acid (35 g.) was esterified by refluxing with methanol (250 c.c.

containing concentrated sulphuric acid (10 g.) for 4 hours. The *ester* distilled at 110—120°/10^{-1} mm. as a mobile, colourless liquid (34 g.) (Found : C, 63·2; H, 9·1. $C_{12}H_{20}O_4$ requires C, 63·2; H, 8·8%).

Formylation of Methyl cyclo*Hexylsuccinate.*—Methyl *cyclo*hexylsuccinate (21 g.) and ethyl formate (12 g.), dissolved in dry ether (200 c.c.), were allowed to react with sodium wire (2·5 g.) at room temperature for 3 days. Water (100 c.c.) was added to dissolve the resinous solid which had been formed, and the aqueous alkaline layer was separated and acidified. The precipitated oil was extracted with ether, the solution washed with dilute sodium carbonate and water, dried, and the solvent removed. The residual oil distilled at 125°/10^{-3} mm. as a colourless liquid (6·8 g.) which gave an intense maroon colour with ferric chloride [Found : C, 61·5; H, 8·0. $C_9H_{14}O(CO_2Me)_2$ requires C, 60·9; H, 7·8%].

*β-Formyl-α-*cyclo*hexylpropionic Acid.*—The above formylation product (6·5 g.) was refluxed with a mixture of glacial acetic acid (25 c.c.) and concentrated hydrochloric acid (15 c.c.) for 3½ hours. The solution, after being partly neutralised with sodium hydroxide, was extracted with ether, and the ethereal solution extracted with aqueous sodium carbonate (10%). The carbonate extract was acidified, and the precipitated oil taken up in ether, the solution dried and evaporated, acetic acid being removed by heating at 100°/12 mm. The residue was distilled in a high vacuum, and the product, a viscous colourless liquid (3·5 g.), b. p. 140—150°/10^{-2} mm., rapidly crystallised in the receiver. Recrystallisation from light petroleum (b. p. 40—60°) gave fine colourless needles, m. p. 66—67°, which reduced Tollens's reagent on warming, but gave no reaction with ferric chloride, or in the Legal reaction (Found : C, 65·3; H, 8·6; equiv., 183. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·7; equiv., 184).

*α-*cyclo*Hexyl-Δ$^{\alpha\beta}$-butenolide.*—The above aldehydo-acid (3·3 g.) was lactonised by refluxing with hydrobromic acid in glacial acetic acid for 4 hours. The reaction mixture was poured into water, extracted with ether, the ethereal extract washed with 5% sodium carbonate solution and water, dried over sodium sulphate, and the solvent removed. The *lactone* distilled at 120°/0·5 mm. as a mobile, colourless liquid (1·67 g.) which reduced Tollens's reagent, and gave a positive Legal reaction (Found : C, 72·6; H, 8·6. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·4%).

Ethyl β-Formyl-β-phenylpropionate.—Dry hydrogen chloride was passed into a stirred suspension of finely powdered anhydrous stannous chloride (57 g.) in dry ether (400 c.c.) until two liquid layers were obtained. Ethyl β-cyano-β-phenylpropionate (40·6 g.; Bredt and Kallen, *Annalen*, 1896, **293**, 343) in ether (30 c.c.) was added slowly with rapid stirring. The mixture was refluxed for 2 hours, resaturated with hydrogen chloride, and allowed to stand overnight. A small amount of solid had separated, and the mixture was refluxed for 8 hours, again saturated with hydrogen chloride, and kept overnight. This was repeated three times. A further quantity of ether (100 c.c.) was then added, and the mixture cooled in ice–salt and saturated with hydrogen chloride. The suspended solid (30 g.) was filtered off, and decomposed by warming to 70° with water (100 c.c.) for 30 mins. The oil which separated was extracted with ether, and the extract washed and dried over sodium sulphate. Removal of the ether left a pale yellow oil (10 g.) which was distilled under reduced pressure. *Ethyl β-formyl-β-phenylpropionate* was obtained as a colourless liquid (7·2 g.), b. p. 85—90°/0·1 mm. (Found : C, 69·4; H, 6·9. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%). It reduced Tollens's reagent at room temperature, but gave no colour in the Legal test. It gave a 2 : 4-*dinitrophenylhydrazone*, which separated from methanol in slender, yellow needles, m. p. 129—130° (Found : C, 56·1; H, 4·7; N, 14·3. $C_{18}H_{18}O_6N_4$ requires C, 56·0; H, 4·7; N, 14·5%).

*β-Phenyl-*Δ$^{\alpha\beta}$*-butenolide.*—Ethyl β-formyl-β-phenylpropionate (2·2 g.) in acetic acid (4 c.c.) was heated under reflux for 2 hours with concentrated hydrochloric acid (4 c.c.). The mixture was cooled, poured into excess of sodium carbonate solution (10%), and extracted with ether. The solvent was removed, and the residual sticky solid recrystallised from aqueous methanol. The lactone separated in colourless prisms, m. p. 97°; Rubin, Paist, and Elderfield (*loc. cit.*) give m. p. 94° (Found : C, 74·7; H, 5·2. Calc. for $C_{10}H_8O_2$: C, 75·0; H, 5·0%). It reduced Tollens's reagent immediately at room temperature, and gave a crimson colour in the Legal test. Light absorption in alcohol : max. at 2730 A. (ε, 20,500).

Ethyl 4-Acetoxybenzylidenemalonate.—*p*-Hydroxybenzaldehyde (6 g.), malonic ester (8 g.), acetic anhydride (12 c.c.), and piperidine (0·2 c.c.) were heated together in a sealed tube at 140—150° for 20 hours. The product was poured into water and the solid which separated was recrystallised from aqueous methanol. *Ethyl 4-acetoxybenzylidenemalonate* formed colourless prisms (7·5 g.), m. p. 67—68° (Found : C, 62·5; H, 5·8. $C_{16}H_{18}O_6$ requires C, 62·7; H, 5·9%).

Ethyl β-Cyano-β-(4-acetoxyphenyl)propionate.—Ethyl 4-acetoxybenzylidenemalonate (36·6 g.) was dissolved in alcohol (250 c.c.) at 30°, and a solution of potassium cyanide (8 g.) in water (15 c.c.) added. The temperature was maintained at 60° for 6 hours, and the precipitate of potassium bicarbonate filtered off (5·3 g.). After standing overnight, the solution was heated to 65° for 4 hours, and a further quantity of bicarbonate (1·8 g.) removed. The solution was then diluted with water (1·5 l.), acidified, and extracted 5 times with ether. The ethereal solution was washed with sodium carbonate and water, dried over sodium sulphate, and the solvent removed. A viscous syrup (24 g.) remained, which was soluble in sodium hydroxide and did not crystallise. The product was therefore acetylated by heating for 30 mins. with acetic anhydride (100 c.c.). The mixture was poured into water and kept until the oil solidified. *Ethyl β-cyano-β-(4-acetoxyphenyl)propionate* crystallised from ether–light petroleum (1 : 1) in feathery needles (24 g.), m. p. 82° (Found : C, 64·2; H, 5·8. $C_{14}H_{15}O_4N$ requires C, 64·3; H, 5·8%). Attempts to reduce this ester by Stephen's method failed to yield any aldehyde.

Ethyl β-Cyano-β-(4-methoxyphenyl)propionate.—Ethyl anisylidenemalonate (25 g.; Knoevenagel and Groos, *Ber.*, 1898, **31**, 2594) in alcohol (150 c.c.) was treated with a solution of potassium cyanide (6 g.) in water (12 c.c.) and heated at 60° for 11 hours. Precipitated potassium bicarbonate (6·3 g.) was filtered off, and the filtrate poured into water and worked up in the usual manner. The *cyano-ester* distilled at 140°/10^{-2} mm. as a colourless liquid (16 g.) (Found : C, 67·6; H, 6·7; N, 5·9. $C_{13}H_{15}O_3N$ requires C, 66·9; H, 6·4; N, 6·0%). Reduction of the ester by Stephen's method gave only traces of aldehyde.

*β-(4-Methoxyphenyl)-*Δ$^{\alpha\beta}$*-butenolide.*—Ethyl bromoacetate (9·2 g.), ω-acetoxy-4-methoxyacetophenone (10·4 g.; Tiffeneau, *Compt. rend.*, 1910, **150**, 1182), and zinc (7 g.) in dry benzene (70 c.c.) were warmed gently until reaction set in. After the initial reaction had subsided, the mixture was refluxed for 2½ hours with stirring. The mixture was then treated with water and dilute hydrochloric acid, and extracted with benzene. The benzene solution was washed, dried over sodium sulphate, and evaporated. The residual yellow oil (6·8 g.), which presumably contained ethyl β-(4-methoxyphenyl)-β-acetoxymethylhydracrylate, was refluxed with a solution of hydrobromic acid in acetic acid for 1 hour to effect lactonisation. The mixture was poured into water, extracted with benzene, the solution dried, and the solvent removed. The residual dark oil (4 g.), heated at 110°/10^{-2} mm., gave a sublimate of crystals mixed with some yellow oil. Crystallisation from benzene yielded pale yellow needles, m. p. 121—122°, which reduced Tollens's reagent and gave a purple colour in the Legal reaction. The absorption spectrum showed maxima at 2250 A. (ε, 16,000) and 3020 A. (ε, 32,000). Marshall, Kuck, and Elderfield (*loc. cit.*) give m. p. 120° for β-(4-methoxyphenyl)-Δ$^{\alpha\beta}$-butenolide prepared by a similar route starting from ω : 4-dimethoxyacetophenone.

β-(4-Hydroxybenzoyl)propionic Acid.—β-(4-Methoxybenzoyl)propionic acid (5 g.) (Rosenmund and Shapiro, *Arch. Pharm.*, 1934, **272**, 318) in a solution of hydrobromic acid in glacial acetic acid (20 c.c. of 33%) was refluxed for 3 hours, and then poured into water. After standing overnight, the dark brown crystalline product was filtered off (1·7 g.) and purified by repeated crystallisation from hot water (charcoal). It was finally recrystallised from benzene–acetone, and obtained as colourless needles, m. p. 159—160° (Found : C, 62·2; H, 5·3. $C_{10}H_{10}O_4$ requires C, 61·9; H, 5·2%).

γ-(4-Acetoxyphenyl)-Δ$^{\beta\gamma}$-butenolide.—A mixture of β-(4-hydroxybenzoyl)propionic acid (8 g.) and acetic anhydride (60 c.c.) was refluxed for 1 hour, and then poured into water. After standing overnight, the solid was filtered off, dried, and sublimed in a vacuum. The sublimate was a white powder, which, however, crystallised from benzene as salmon-pink needles. Resublimation gave colourless needles (2·8 g.), m. p. 123—124° (Found: C, 66·3; H, 4·9. $C_{12}H_{10}O_4$ requires C, 66·1; H, 4·6%). The substance reduced Tollens's reagent, and gave a positive Legal reaction. The absorption spectrum in alcohol showed a maximum at 2650 A. (ε, 13,000).

γ-(4-Methoxyphenyl)-Δ$^{\beta\gamma}$-butenolide.—β-(4-Methoxybenzoyl)propionic acid (1·5 g.) and acetic anhydride (5 c.c.) were refluxed for 1½ hours, and then poured into water. After standing for a short time the red solid was collected, dissolved in ether, and the solution washed with sodium bicarbonate solution and then with water, dried, and the solvent removed. The residue sublimed at 100°/5 × 10^{-3} mm. as a white solid (0·6 g.). Attempts to purify it by crystallisation from ordinary solvents were unsatisfactory on account of gradual decomposition. It was finally obtained as a white crystalline powder, m. p. 110°, by repeated vacuum sublimation (Found: C, 68·7; H, 5·1; CH_3O, 16·1. $C_{11}H_{10}O_3$ requires C, 69·5; H, 5·3; CH_3O, 16·3%). It reduced Tollens's reagent in the cold, and the Legal test produced a transient green coloration passing rapidly through brown to deep red.

2-Ethoxy-6-naphthoylpropionic Acid, 2-Ethoxy-1-naphthoylpropionic Acid, and 2-Hydroxy-6-naphthoylpropionic Acid.—Aluminium chloride (80 g., 2 mols.) was powdered and dissolved in nitrobenzene (260 g.), and the solution cooled to 10°. Finely powdered succinic anhydride (33 g., 1·1 mols.) was stirred in, and the mixture cooled to 0° in an ice-salt bath. 2-Ethoxynaphthalene (51·6 g., 1 mol.), dissolved in nitrobenzene (65 c.c.) at 10°, was added to the stirred mixture during 1½ hours. Stirring was continued at 0° for 2 hours, and at room temperature for a further 5 hours. After standing for 3 days, the green oil was poured on a mixture of ice (500 g.) and hydrochloric acid (200 c.c., *d* 1·16), and the mixture was then warmed to 40° in order to facilitate separation of the nitrobenzene from the aqueous layer which was rejected. The nitrobenzene was removed in steam, and the green viscous residue dissolved in sodium carbonate solution (300 c.c. of 10%) at 35°. Salt (100 g.) was added but the precipitated sodium salts could not be filtered off satisfactorily, and were therefore redissolved by addition of water (500 c.c.). The solution, containing a little suspended material, was washed thrice with ether. Some solid separated at the interface and was removed by filtration (A). This solid was dissolved in water, the solution filtered, and the filtrate acidified. The white, crystalline solid which separated (3·9 g.) was recrystallised from aqueous alcohol (60%) and finally from alcohol. 2-Hydroxy-6-naphthoylpropionic acid was obtained in small, colourless plates, m. p. 229—231° (Found: C, 69·0; H, 4·9. Calc. for $C_{14}H_{12}O_4$: C, 68·8; H, 5·0%). Robinson and Thompson (J., 1938, 2012) give m. p. 235°. The 2 : 4-*dinitrophenylhydrazone* separated from benzene–alcohol (1 : 1) in small red prisms, m. p. 216—217° (Found: N, 12·8. $C_{20}H_{16}O_7N_4$ requires N, 13·2%).

The aqueous filtrate after removal of (A) was acidified with concentrated hydrochloric acid and the oily brown solid which separated was collected, washed with water, and the moist filter cake dissolved in hot methanol (180 c.c.). On cooling, brown prisms (24·5 g.; m. p. 135—140°) were deposited. Recrystallisation from ethyl acetate (charcoal) gave *2-ethoxy-6-naphthoylpropionic acid* (14 g.) as colourless prisms, m. p. 162—163° (Found: C, 71·1; H, 6·0. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%). It was characterised as the 2 : 4-*dinitrophenylhydrazone*, which separated from ethyl acetate in orange-red, feathery needles, m. p. 171—172° (Found: N, 11·6. $C_{22}H_{20}O_7N_4$ requires N, 12·4%).

Concentration of the methanolic mother-liquors yielded a further small amount of slightly oily crystalline solid (5·6 g., m. p. 125—130°). This was recrystallised, the solvent being the ethyl acetate mother-liquors of the 2-ethoxy-6-naphthoylpropionic acid, and, by fractionation, *2-ethoxy-1-naphthoylpropionic acid* (5·0 g.) was finally obtained in colourless prisms, m. p. 164—165° (depression to 140° in admixture with the 2 : 6-isomer) (Found: C, 70·7; H, 6·1. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%). No 2 : 4-dinitrophenylhydrazone could be obtained. A specimen of 2-methoxy-1-naphthoylpropionic acid (kindly supplied by Dr. W. F. Short) did not form a 2 : 4-dinitrophenylhydrazone under similar conditions.

De-ethylation of 2-Ethoxy-6-naphthoylpropionic Acid.—The ethoxy-acid (1·0 g.) was heated under reflux for 3½ hours with aqueous acetic acid (10 c.c. of acid + 5 c.c. of water) and hydrobromic acid (10 c.c. of a 50% solution in acetic acid). On cooling, the reddish-brown solution deposited a solid (0·7 g.), which was recrystallised first from aqueous alcohol and finally from alcohol–ethyl acetate. 2-Hydroxy-6-naphthoylpropionic acid separated in small colourless plates, m. p. 229—231°, undepressed in admixture with the specimen already described.

De-ethylation of the isomeric 2-ethoxy-1-naphthoylpropionic acid in a similar manner gave β-naphthol, m. p. 120—121°. 2-Methoxy-1-naphthoylpropionic acid behaved in exactly the same way.

γ-(2-Acetoxy-6-naphthyl)-Δ$^{\beta\gamma}$-butenolide.—2-Hydroxy-6-naphthoylpropionic acid (1·0 g.) was refluxed for 2 hours with acetic anhydride (10 c.c.). The solution became deep orange red. Acetic anhydride was decomposed by addition of excess of water, and the reddish-brown precipitated solid was filtered off, washed with water, dried, and sublimed at 120—140°/10^{-4} mm. The colourless crystalline sublimate (0·4 g., m. p. 135—142°) was recrystallised from ethyl acetate, giving *γ-(2-acetoxy-6-naphthyl)-Δ$^{\beta\gamma}$-butenolide* as faintly pink plates, m. p. 158—160° (sintering at 150°) (Found: C, 72·2; H, 4·5. $C_{16}H_{12}O_4$ requires C, 71·7; H, 4·5%). The lactone reduced Tollens's reagent immediately at room temperature and gave a crimson colour in the Legal test. It became coloured on exposure to light and air or on boiling its solutions in common organic solvents—especially in alcohol.

Our thanks are due to Messrs. Imperial Chemical Industries Limited for their support of this investigation.

THE UNIVERSITY, MANCHESTER. [*Received, August 23rd,* 1944.]

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153. *Polycyclic Aromatic Hydrocarbons. Part XXIX. Derivatives of* 1 : 2 : 5 : 6-*Dibenzfluorene.*

By J. W. COOK and ROBERT W. G. PRESTON.

A series of derivatives of 1 : 2 : 5 : 6-dibenzfluorene (I) has been prepared directly from this hydrocarbon and from 1 : 2 : 5 : 6-dibenzfluorenone, in an endeavour to find compounds more inhibitory to tumour growth than the parent hydrocarbon. Two new synthetical routes to derivatives of 1 : 2 : 5 : 6-dibenzfluorene have been devised. One of these, starting from 2-benzoylnaphthalene, leads to compounds of types (X) and (XI). This method involves ring-closure of the acid (IV) to the *keto-acid* (V). A second *keto-acid* formed in this cyclisation is believed to have the structure (VI) and has been converted into pentacyclic compounds probably derived from 3 : 4-(1′ : 2′-naphtha)fluorene. The second method consists in *cyclo*-dehydrogenation of *4-(2′-naphthoyl)-1-methoxynaphthalene* (XV) to *3-hydroxy-1 : 2 : 5 : 6-dibenzfluorenone* (XVI) by fusion with aluminium chloride.

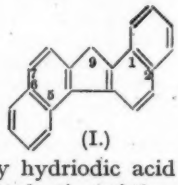
1 : 2 : 6 : 7-*Dibenzfluorene* has also been prepared, and some possible synthetical routes to the unknown

2 : 3-(2′ : 1′-naphtha)fluorene (XVIII) have been explored. 9 : 10-Dihydrophenanthrene was found to undergo chloromethylation at position 3, although in Friedel–Crafts reactions the substituent enters at position 2.

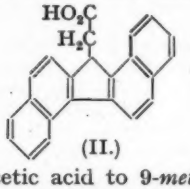
1 : 2 : 5 : 6-DIBENZFLUORENE (I) has feeble cancer-producing activity (Bachmann, Cook, Dansi, de Worms, Haslewood, Hewett, and Robinson, *Proc. Roy. Soc.*, 1937, *B*, **123**, 343) and has also a very pronounced effect in inhibiting the growth of tumours (Haddow and Robinson, *ibid.*, 1939, *B*, **127**, 277). As part of a search for compounds having still more marked growth-inhibitory activity a series of derivatives of 1 : 2 : 5 : 6-dibenzfluorene has been prepared. By the synthetic method of Swain and Todd (J., 1941, 674) it was possible to obtain the hydrocarbon in sufficient quantity to prepare some of its derivatives by direct substitution. Biological tests carried out by Dr. Haddow on many of these will be reported elsewhere.

A *monosulphonic acid* and a *mononitro*-compound were readily obtained from 1 : 2 : 5 : 6-dibenzfluorene. The nitro-compound was reduced to *amino*-1 : 2 : 5 : 6-*dibenzfluorene* and was oxidised by selenious acid to a *nitro*-1 : 2 : 5 : 6-*dibenzfluorenone* which was also obtained by direct nitration of 1 : 2 : 5 : 6-dibenzfluorenone. This nitro-ketone was reduced by stannous chloride to *amino*-1 : 2 : 5 : 6-*dibenzfluorenone*. By analogy with substitution reactions of fluorene and fluorenone, it is probable that in all these derivatives the substituent is at position 7, which is the only free position *para* to the bond joining the two naphthalene nuclei, and is also an α-position of a naphthalene system. This orientation has not been proved, however, for, although 7-substituted derivatives of 1 : 2 : 5 : 6-dibenzfluorene have been prepared by an independent synthesis described below, it has not been possible to corrrelate them with the compounds obtained by direct substitution. All attempts to effect replacement of the amino-group in amino-1 : 2 : 5 : 6-dibenzfluorene by a hydroxyl group were unsuccessful.

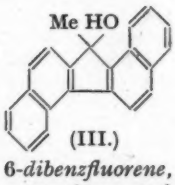
A series of 9-substituted derivatives of 1 : 2 : 5 : 6-dibenzfluorene has also been prepared. Reduction of 1 : 2 : 5 : 6-dibenzfluorenone by zinc in acetic acid (compare Wanscheidt, *Ber.*, 1926, **59**, 2096) gave 1 : 2 : 5 : 6-*dibenz*-9-*fluorenol*, from which 9-*bromo*-1 : 2 : 5 : 6-*dibenzfluorene* was obtained by means of hydrogen bromide. This bromo-compound could not be satisfactorily condensed with ethyl malonate. The desired 1 : 2 : 5 : 6-*dibenzfluorenyl*-9-*acetic acid* (II) was obtained by reduction of the crude hydroxy-ester resulting from interaction of 1 : 2 : 5 : 6-dibenzfluorenone with ethyl bromoacetate in presence of zinc. By treatment of 1 : 2 : 5 : 6-dibenzfluorenone with methylmagnesium iodide the tertiary *carbinol* (III) was readily formed. This carbinol



(I.)



(II.)



(III.)

was reduced by hydriodic acid in boiling acetic acid to 9-*methyl*-1 : 2 : 5 : 6-*dibenzfluorene*, which was not obtained by dehydration of the carbinol followed by hydrogenation, a procedure used successfully in analogous cases (Fieser and Joshel, *J. Amer. Chem. Soc.*, 1940, **62**, 957; Badger, J., 1941, 535). Condensation of 1 : 2 : 5 : 6-dibenzfluorenone with ethylmagnesium bromide gave capricious results, and 9-ethyl-1 : 2 : 5 : 6-dibenzfluorene has not been obtained.

An *acetyl*-1 : 2 : 5 : 6-*dibenzfluorene* of unknown orientation resulted from treatment of the hydrocarbon with acetyl chloride and aluminium chloride. The corresponding carboxylic acid could not be obtained by oxidation with sodium hypochlorite.

For the production of a hydroxy-1 : 2 : 5 : 6-dibenzfluorene of known structure, a new ring-synthesis of the 1 : 2 : 5 : 6-dibenzfluorene ring system was devised.* The starting point was the γ-phenyl-γ-2-naphthylitaconic acid (IV) which Hewett (J., 1942, 585) obtained by hydrolysis of the condensation product of 2-benzoylnaphthalene and ethyl succinate. Theoretically, monocyclisation of acids of this type might give either a 5- or a 6-membered ring, depending upon which carboxyl group is involved. Actually, the 5-membered ring appears to be formed exclusively (Stobbe and Vieweg, *Ber.*, 1902, **35**, 1727; Haworth and Sheldrick, J., 1935, 636) and this was found to be the case with γ-phenyl-γ-2-naphthylitaconic acid (IV), the anhydride of which was converted by aluminium chloride in nitrobenzene into a mixture of two orange keto-acids, 1-*keto*-3-*phenyl*-6 : 7-*benzindene*-2-*acetic acid* (V) and 1-*keto*-3-(2′-*naphthyl*)*indene*-2-*acetic acid* (VI).

These two acids were converted by ethereal diazomethane into their normal *methyl* esters, m. p. 136° and 98°, respectively. Esterification by the Fischer–Speier method gave two isomeric *methyl* esters, m. p. 84° and 102°, respectively. Like the parent acids, these four esters are deeply coloured. The two *pseudo*-esters are regarded as methoxy-lactones (VII and VIII). Similar *pseudo*-esters of derivatives of 2-benzoylbenzoic acid have been described (Newman *et al.*, *J. Amer. Chem. Soc.*, 1941, **63**, 1537; 1944, **66**, 731). The structure of a hydroxy-lactone corresponding with (VII) is suggested by Hewett for a product which he obtained by dehydration of γ-phenyl-γ-2-naphthylitaconic acid (IV) with concentrated sulphuric acid. In view of the lack of colour in Hewett's lactone, we regard his alternative structure (IX) as more probable.

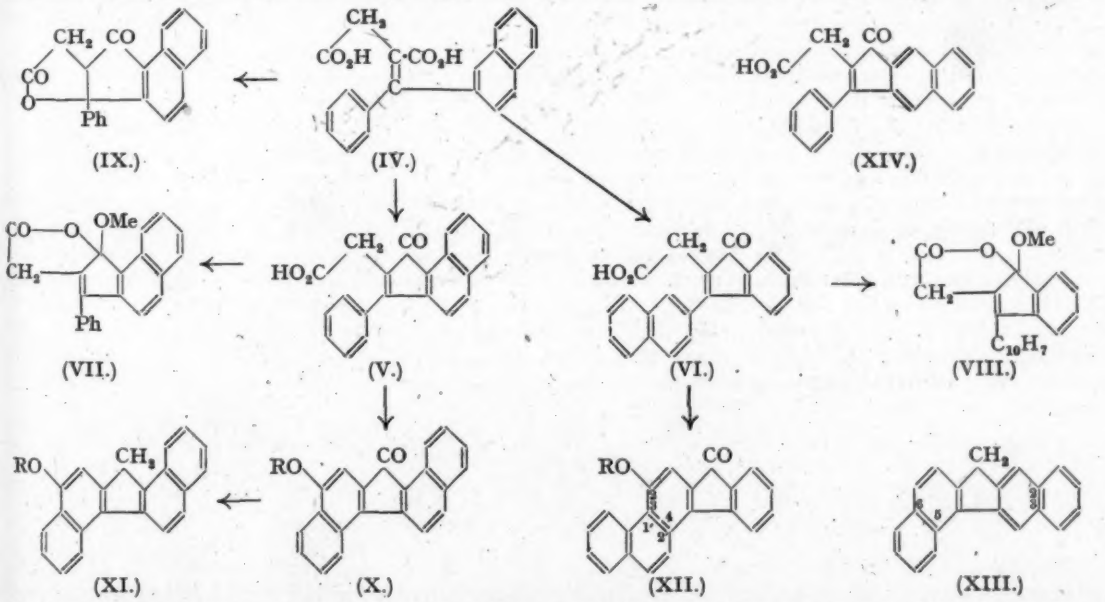
When 1-keto-3-phenyl-6 : 7-benzindene-2-acetic acid (V) was treated with boiling acetic anhydride it underwent cyclisation to the dark red 7-*acetoxy*-1 : 2 : 5 : 6-*dibenzfluorenone* (X; R = COMe), hydrolysed by alcoholic potash to the purplish-black 7-*hydroxy*-1 : 2 : 5 : 6-*dibenzfluorenone* (X; R = H). This phenol gave 1 : 2 : 5 : 6-

* (*Added in proof.*) Our attention has been called to the prior use by Borsche (*Annalen*, 1936, **526**, 1) of the same type of method for the synthesis of 2-hydroxy-3 : 4-benzfluorenone from γγ-diphenylitaconic acid.

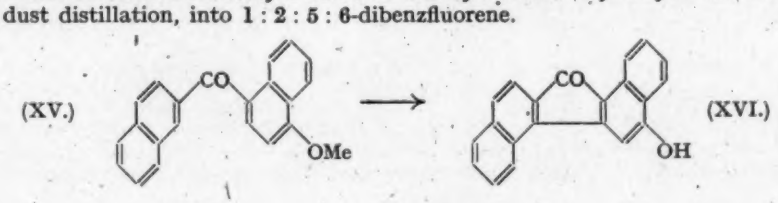
dibenzfluorene when distilled with zinc dust, and was reduced by zinc and acetic acid, followed by hydriodic acid, to *7-hydroxy*-1 : 2 : 5 : 6-*dibenzfluorene* (XI; R = H). An attempt to convert this into 7-amino-1 : 2 : 5 : 6-dibenzfluorene, for comparison with the amino-compound prepared from nitrated 1 : 2 : 5 : 6-dibenzfluorene, was unsuccessful.

1-Keto-3-(2′-naphthyl)indene-2-acetic acid (VI) was converted by boiling acetic anhydride into an *acetoxyketone* to which we attribute tentatively the structure (XII; R = COMe). This is based on the probability that ring-closure would take place in the α- rather than the β-position of the naphthalene system. The acetoxyketone was hydrolysed to the phenol (XII; R = H), from which was obtained, by distillation with zinc dust, a small amount of a compound, m. p. 189° [presumably 3 : 4-(1′ : 2′-naphtha)fluorene]. On auto-oxidation in potassium methoxide solution, this passed into an orange-brown substance, m. p. 155° [presumably 3 : 4-(1′ : 2′-naphtha)fluorenone].

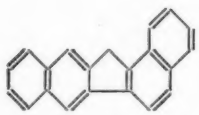
The keto-acid (VI) obtained by mono-ring closure of γ-phenyl-γ-2-naphthylitaconic acid (IV) might have the alternative structure (XIV). This would lead, by the reactions outlined in the preceding paragraph, to 2 : 3 : 5 : 6-dibenzfluorene (XIII) and the corresponding fluorenone. Schmidlin and Huber (*Ber.*, 1910, **43**, 2824) obtained, as a by-product in the preparation of di-2-naphthylcarbinol, a hydrocarbon, m. p. 186°, which they oxidised by chromic acid to an orange-red ketone, m. p. 160—162°. If these compounds are fluorene derivatives, as Schmidlin and Huber postulated, they must have the 2 : 3 : 5 : 6-dibenz-structure (XIII) (compare Martin, J., 1941, 679). Their melting points are in reasonable agreement with those of the two compounds mentioned at the end of the preceding paragraph. However, Lothrop and Goodwin (*J. Amer. Chem. Soc.*, 1943, **65**, 363) have recently synthesised 2 : 3 : 5 : 6-dibenzfluorenone and found it to have m. p. 185°; they suggested that the compounds of Schmidlin and Huber were 2 : 2′-dinaphthyl and its quinone, a view to which we subscribe in spite of its inconsistency with the analytical figures quoted by Schmidlin and Huber for their oxidation product. These are the considerations which lead us to adopt structure (VI) in preference to the alternative structure (XIV) for one of the two keto-acids obtained by cyclisation of the acid (IV). This is admittedly inconclusive, for the amounts of the compounds obtained by zinc dust distillation of the phenol (XII; R = H), followed by auto-oxidation, were insufficient for analysis.



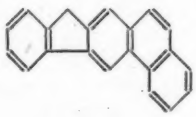
Another synthetic approach to derivatives of 1 : 2 : 5 : 6-dibenzfluorene was suggested by the finding of Fierz-David and Jaccard (*Helv. Chim. Acta*, 1928, **11**, 1042) that the Scholl ring-closure of 1-methoxy-4-benzoylnaphthalene gives 3-hydroxy-1 : 2-benzfluorenone and not the isomeric *meso*benzanthrone derivative. We have improved the conditions for obtaining this hydroxybenzfluorenone, and have confirmed its structure by converting it by zinc dust distillation into 1 : 2-benzfluorene, identical with an authentic specimen. Extension of this reaction to *1-methoxy-4-(2′-naphthoyl)naphthalene* (XV) gave *3-hydroxy*-1 : 2 : 5 : 6-*dibenzfluorenone* (XVI), which was converted into *3-acetoxy*-1 : 2 : 5 : 6-*dibenzfluorenol*, *3-hydroxy*-1 : 2 : 5 : 6-*dibenzfluorene*, and thence, by zinc dust distillation, into 1 : 2 : 5 : 6-dibenzfluorene.



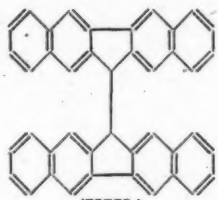
Promising results obtained by Dr. Haddow in tests for growth-inhibitory action carried out with certain polycyclic nitrogenous compounds suggested examination of their carbocyclic analogues, 1 : 2 : 6 : 7-dibenzfluorene (XVII) and 2 : 3-(2′ : 1′-naphtha)fluorene (XVIII). 1 : 2 : 6 : 7-Dibenzfluorenone, prepared by the method of Martin (*loc. cit.*), could not be reduced to the fluorenol with zinc and acetic acid, which gives good results with other fluorenones, or by magnesium and methyl alcohol. 1 : 2 : 6 : 7-*Dibenzfluorenol* was readily obtained, however, by Pondorff reduction of the ketone, and was converted by hydrogen bromide into 9-*bromo*-1 : 2 : 6 : 7-*dibenzfluorenol*. The yield of 1 : 2 : 6 : 7-*dibenzfluorene* obtained by reduction of 1 : 2 : 6 : 7-dibenzfluorenone by hydrazine hydrate in a sealed tube was much influenced by the amount of hydrazine hydrate used. Under suitable conditions good yields were obtained, but with excess of hydrazine hydrate a considerable proportion of the ketone was converted into by-products, apparently chiefly the azine. In the similar reduction of 2 : 3 : 6 : 7-dibenzfluorenone (cf. Martin, *loc. cit.*) there were obtained, in addition to 2 : 3 : 6 : 7-dibenzfluorene, 2 : 3 : 6 : 7 : 2′ : 3′ : 6′ : 7′-*tetrabenz*-9 : 9′-*difluorenyl* (XIX) and the corresponding *azine* (XX).



(XVII.)



(XVIII.)



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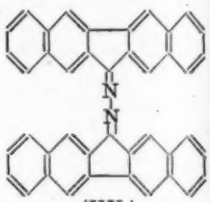
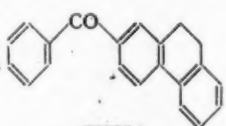


(XX.)

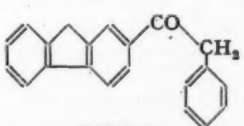
2 : 3-(1′ : 2′-Naphtha)fluorene has been synthesised by a method which involves condensation of 3-chloromethylphenanthrene with ethyl *cyclo*hexanone-2-carboxylate (J., 1935, 1319). As 9 : 10-dihydrophenanthrene normally undergoes substitution at position 2 (Burger and Mosettig, *J. Amer. Chem. Soc.*, 1935, **57**, 2731; 1936, **58**, 1857) it was anticipated that 2-chloromethyl-9 : 10-dihydrophenanthrene could be obtained by chloromethylation of dihydrophenanthrene, and used for a similar synthesis of 2 : 3-(2′ : 1′-naphtha)fluorene (XVIII). The liquid product of chloromethylation consisted essentially, however, of 3-chloromethyl-9 : 10-dihydrophenanthrene as it was hydrolysed, through its acetate, to a *carbinol*, m. p. 89—92°, whereas 2-hydroxymethyl-9 : 10-dihydrophenanthrene has m. p. 77—78° (*idem*, *J. Amer. Chem. Soc.*, 1937, **59**, 1305). Moreover, reduction, followed by dehydrogenation, of the chloromethyl compound gave 3-methylphenanthrene.

Recourse was had, therefore, to a Friedel–Crafts reaction between benzoyl chloride and 9 : 10-dihydrophenanthrene. This gave a liquid mixture, of which the principal constituent was 2-*benzoyl*-9 : 10-*dihydrophenanthrene* (XXI), a pure sample of which was prepared by condensation of 9 : 10-dihydro-2-phenanthroyl chloride with benzene. Reduction of the crude ketone with sodium amyloxide gave an oil which probably consisted mainly of the carbinol corresponding with (XXI), but cyclisation of this carbinol to a fluorene derivative with metaphosphoric acid or succinic anhydride could not be accomplished (compare Martin, *loc. cit.*).

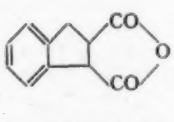
We have explored other possible routes to 2 : 3-(2′ : 1′-naphtha)fluorene (XVIII). 2-Phenylacetylfluorene (XXII) was submitted to the conditions of an Elbs pyrolytic synthesis of anthracene hydrocarbons but gave no useful result. The corresponding 2-β-phenylethylfluorene might undergo *cyclo*-dehydrogenation by aluminium chloride (compare Ruzicka and Hösli, *Helv. Chim. Acta*, 1934, **17**, 470), but in view of the uncertain structures of the *products* obtained by Clemmensen reduction of 2-phenylacetylfluorene (XXII) this project was dropped.



(XXI.)



(XXII.)



(XXIII.)

In a final attempt to synthesise the desired hydrocarbon, ethyl indene-2 : 3-dicarboxylate was prepared by the method of Bougault (*Compt. rend.*, 1914, **159**, 745) and converted into the *anhydride* (XXIII) of *cis*-indane-1 : 2-dicarboxylic acid. This work had to be interrupted before it was possible to study the interaction of this anhydride with β-naphthylmagnesium bromide.

Experimental.

7(?)-*Nitro*-1 : 2 : 5 : 6-*dibenzfluorene*.—A mixture of nitric acid (*d* 1·5; 0·63 c.c.) and acetic acid was added dropwise to a stirred suspension of 1 : 2 : 5 : 6-dibenzfluorene (4 g.) in acetic acid (50 c.c.). After an hour, the brownish solid in suspension was collected and washed with acetic acid and then methyl alcohol. The *nitro-compound* (3·5 g.) crystallised from xylene in orange needles, m. p. 184—185° (Found : C, 81·0; H, 4·1; N, 4·7. $C_{21}H_{13}O_2N$ requires C, 81·0; H, 4·2; N, 4·5%).

7(?)-*Amino*-1 : 2 : 5 : 6-*dibenzfluorene* was obtained when a solution of stannous chloride (10 g.) in concentrated hydrochloric acid (40 c.c.) was added slowly to a boiling suspension of the nitro-compound (3 g.) in acetic acid (120 c.c.), boiling being continued for an hour after the addition. The resulting solid was collected, extracted with boiling sodium hydroxide solution, and crystallised from benzene (yield, 2 g.). A sample, sublimed in a high vacuum at 180° and crystallised from benzene, formed yellowish needles, m. p. 245—249°, after sintering at 241° (Found : C, 89·7; H, 5·4; N, 5·2. $C_{21}H_{15}N$ requires C, 89·7; H, 5·3; N, 5·0%). The *diacetylamino*-compound crystallised when a solution of this amine

(0·1 g.) in acetic anhydride (3 c.c.) was boiled for 3 minutes, and the solution cooled. It formed brownish prisms (from ethyl acetate), m. p. 245—250° (decomp.) (Found : C, 82·1; H, 5·6. $C_{23}H_{19}O_4N$ requires C, 82·2; H, 5·2%).

Unsuccessful attempts were made to convert the amino-1 : 2 : 5 : 6-dibenzfluorene into the corresponding hydroxy-compound through the diazo-compound, and also by heating it in a sealed tube at 190° with 10% sulphuric acid (compare Newman and Cathcart, *J. Org. Chem.*, 1940, **5**, 621). Methods used for diazotisation included (*a*) addition of sodium nitrite solution to a suspension of amine in hydrochloric acid, (*b*) addition of solid sodium nitrite to a solution of the amine in concentrated sulphuric acid, and (*c*) treatment in pyridine solution with nitrosylsulphuric acid (compare de Milt and van Zandt, *J. Amer. Chem. Soc.*, 1936, **58**, 2044).

1 : 2 : 5 : 6-*Dibenzfluorene*-7(?)-*sulphonic acid*.—A solution of concentrated sulphuric acid (1·8 c.c.) in acetic anhydride (18 c.c.) was slowly added to a stirred ice-cold suspension of 1 : 2 : 5 : 6-dibenzfluorene (3 g.) in acetic anhydride (150 c.c.). The mixture was kept overnight in the refrigerator, and the suspended solid collected and washed with dry ether. The *sulphonic acid*, crystallised from acetic acid and then ethyl acetate, formed colourless needles, m. p. 112—120° (decomp.) (Found : C, 72·7; H, 4·1. $C_{21}H_{14}O_3S$ requires C, 72·8; H, 4·05%). The sparingly soluble sodium salt darkens on exposure to light.

7(?)-*Nitro*-1 : 2 : 5 : 6-*dibenzfluorenone*.—(*a*) Nitric acid (*d* 1·5; 0·6 c.c.) was added dropwise to a stirred suspension of 1 : 2 : 5 : 6-dibenzfluorenone (0·5 g.) in acetic acid (8 c.c.). After 10 minutes the solid was collected, dried, and recrystallised from xylene, in which it was very sparingly soluble. This *nitro-ketone* formed fine red needles, m. p. 324—326° (Found : N, 4·3. $C_{21}H_{11}O_3N$ requires N, 4·3%).

(*b*) Nitro-1 : 2 : 5 : 6-dibenzfluorene (0·16 g.), prepared by nitrating the hydrocarbon, was heated at 230° for 6 hours in a sealed tube with selenium dioxide (0·3 g.) in water (0·3 c.c.). The product, after several recrystallisations from xylene, formed red needles (0·05 g.), m. p. 308—312°, not depressed by admixture with a specimen prepared as described under (*a*).

7(?)-*Amino*-1 : 2 : 5 : 6-*dibenzfluorenone*.—A mixture of the nitro-ketone (0·3 g.), xylene (100 c.c.), and a solution of stannous chloride (6 g.) in concentrated hydrochloric acid (60 c.c.) was boiled under reflux for 20 hours. The resulting tin complex was extracted with boiling alkali, and the insoluble residue was recrystallised from xylene, forming black needles (0·12 g.), m. p. 265—270° (Found : C, 85·55; H, 4·8. $C_{21}H_{13}ON$ requires C, 85·4; H, 4·4%).

1 : 2 : 5 : 6-*Dibenz*-9-*fluorenol*.—A solution of 1 : 2 : 5 : 6-dibenzfluorenone (2 g.) in acetic acid (200 c.c.) was boiled with zinc filings (2 g.) for 45 minutes. The *carbinol* was precipitated with water and crystallised from benzene, forming almost colourless needles (1·5 g.), m. p. 201—202° (Found : C, 89·2; H, 4·9. $C_{21}H_{14}O$ requires C, 89·4; H, 5·0%).

9-*Bromo*-1 : 2 : 5 : 6-*dibenzfluorene*.—A hot solution of 1 : 2 : 5 : 6-dibenz-9-fluorenol (0·1 g.) in acetic acid (10 c.c.) was saturated with hydrogen bromide. The *bromo*-compound, which crystallised on cooling, formed yellow needles (from benzene), m. p. 197—199° (Found : Br, 23·4. $C_{21}H_{13}Br$ requires Br, 23·2%). In the preparation of this bromo-compound from 1 : 2 : 5 : 6-dibenzfluorenone, isolation of the intermediate carbinol was unnecessary. It was sufficient to pass in hydrogen bromide after reduction of the ketone with zinc and acetic acid.

1 : 2 : 5 : 6-*Dibenzfluorenyl*-9-*acetic acid* (II).—Condensation of the bromo-compound with ethyl sodiomalonate in benzene–alcohol appeared to take place, but when the crude product was hydrolysed and the acid heated to 180° profound decomposition took place. The only crystalline product isolated appeared to be 1 : 2 : 5 : 6-dibenzfluorenone. The acetic acid (II) was obtained as follows. Pure zinc filings (2·5 g.) were added to a mechanically stirred solution of 1 : 2 : 5 : 6-dibenzfluorenone (1·5 g.) in dry benzene (150 c.c.) containing ethyl bromoacetate (4 c.c.) and pyridine (1 c.c.), and the mixture was boiled until reaction set in. Boiling was continued for 1½ hours, and the solution decanted into ice and dilute sulphuric acid. The benzene layer was separated, dried, and the solvent removed. As alkaline hydrolysis led to auto-oxidation to dibenzfluorenone, the crude hydroxy-ester was submitted to reductive hydrolysis by boiling for 2 hours with acetic acid (40 c.c.) and hydriodic acid (*d* 1·95; 5 c.c.). The 1 : 2 : 5 : 6-*dibenzfluorenyl*-9-*acetic acid* (II), precipitated by pouring into ice-cold sulphurous acid, crystallised from toluene in colourless needles (1·1 g.), m. p. 221—223° (Found : C, 85·6; H, 5·5. $C_{23}H_{16}O_2$ requires C, 85·2; H, 4·9%). The sparingly soluble sodium salt crystallised from water in microscopic needles. The *methyl* ester, prepared by treatment of the acid with ethereal diazomethane, formed pale yellow needles (from alcohol), m. p. 127—128° (Found : C, 84·9; H, 5·3. $C_{24}H_{18}O_2$ requires C, 85·2; H, 5·3%).

9-*Methyl*-1 : 2 : 5 : 6-*dibenzfluorene*.—A solution of 1 : 2 : 5 : 6-dibenzfluorenone (2 g.) in dry benzene (100 c.c.) was added to a stirred Grignard solution prepared from methyl iodide (4·5 g.) and magnesium (0·7 g.). After being kept overnight at room temperature, the ether was distilled, and the residual benzene solution was boiled for 2 hours. The cooled solution was treated with ice and ammonium chloride, and the benzene solution was washed, dried, and evaporated. The residual oil crystallised from benzene–ligroin in yellow rectangular prisms (1·7 g.), m. p. 131—132°, of 9-*methyl*-1 : 2 : 5 : 6-*dibenz*-9-*fluorenol* (III) (Found : C, 89·2; H, 5·5. $C_{22}H_{16}O$ requires C, 89·2; H, 5·4%).

A solution of this carbinol (1·4 g.) in acetic acid (70 c.c.) and hydriodic acid (*d* 1·95; 7 g.) was boiled for 3 hours. The yellow precipitate formed by pouring into ice-cold sulphurous acid was collected, dried, and sublimed at 120° in a high vacuum. 9-*Methyl*-1 : 2 : 5 : 6-*dibenzfluorene* (1·2 g.) crystallised from alcohol in colourless plates, m. p. 144—145° (Found : C, 94·3; H, 5·6. $C_{22}H_{16}$ requires C, 94·3; H, 5·7%). The *bis*-1 : 3 : 5-*trinitrobenzene* complex, prepared in alcoholic solution, formed orange needles (from benzene–*cyclo*hexane), m. p. 139·5—140·5° (Found : N, 12·1. $C_{22}H_{16}.2C_6H_3O_6N_3$ requires N, 11·9%).

9-*Ethyl*-1 : 2 : 5 : 6-*dibenz*-9-*fluorenol*.—A solution of 1 : 2 : 5 : 6-dibenzfluorenone (0·7 g.) in dry benzene (50 c.c.) was added to ethereal ethylmagnesium bromide (from 0·25 g. of magnesium and 1·25 g. of ethyl bromide). The mixture was stirred at room temperature for ½ hour, the ether distilled off, and the benzene solution boiled for 14 hours. After decomposition with ice and ammonium chloride, the tertiary *carbinol* was isolated as colourless prisms (0·4 g.) (from methyl alcohol), m. p. 151° (Found : C, 88·7; H, 6·05. $C_{23}H_{18}O$ requires C, 89·0; H, 5·8%). Repetition of this experiment gave an unsatisfactory yield.

Acetyl-1 : 2 : 5 : 6-*dibenzfluorene*.—A solution of anhydrous aluminium chloride (2 g.) in nitrobenzene (20 c.c.) was added to a solution of 1 : 2 : 5 : 6-dibenzfluorene (2 g.) in nitrobenzene (10 c.c.), and the ice-cooled mixture was treated with acetyl chloride (0·7 c.c.), stirred for 4 hours (1 hour at 0°; 3 hours at room temperature), and then kept without stirring for 16 hours. The product was decomposed with ice and hydrochloric acid, the nitrobenzene removed in steam, and the residue extracted with chloroform. The material obtained from the dried chloroform extract was crystallised twice from benzene and then from alcohol, forming straw-coloured needles (1·2 g.), m. p. 146—146·5° (Found : C, 89·4; H, 5·2. $C_{25}H_{16}O$ requires C, 89·6; H, 5·2%). This *acetyl*-1 : 2 : 5 : 6-*dibenzfluorene* gave, with hydroxylamine hydrochloride in pyridine at 100°, an *oxime*, which crystallised from benzene in straw-coloured needles, m. p. 209—212° (Found : C, 84·9; H, 5·6. $C_{23}H_{17}ON$ requires C, 85·45; H, 5·3%).

1-*Keto*-3-*phenyl*-6 : 7-*benzindene*-2-*acetic Acid* (V) *and* 1-*Keto*-3-(2′-*naphthyl*)*indene*-2-*acetic Acid* (VI).—γ-Phenyl-γ-2-naphthylitaconic acid (IV) (Hewett, *loc. cit.*) was esterified by 4 hours' boiling with methyl alcohol saturated in the cold with hydrogen chloride. The resulting *methyl* ester crystallised from methyl alcohol in colourless plates, m. p. 125—126° (Found : C, 76·4; H, 5·6; OMe, 17·4. $C_{25}H_{20}O_4$ requires C, 76·7; H, 5·6; OMe, 17·2%). Another experiment, under the same conditions, gave the methyl ester, m. p. 94—95°, obtained by Hewett by esterification of the acid with

diazomethane. This lower-melting ester was not changed by boiling its solution in methyl-alcoholic hydrogen chloride for 6 hours. The reason for the formation of the higher-melting ester in the earlier experiment is obscure.

The anhydride of γ-phenyl-γ-2-naphthylitaconic acid (40 g.) was prepared by boiling under reflux for 2 hours with acetyl chloride (80 g.). The solvent was removed, and the anhydride, dissolved in nitrobenzene (400 c.c.), was treated slowly at 0° with anhydrous aluminium chloride (40 g.). The mixture was kept at 0° for 24 hours, then decomposed with ice and hydrochloric acid, and the nitrobenzene removed in steam. The residue was extracted with ether and the ethereal extract shaken with a very large volume of sodium carbonate solution (about 0·25N). The ethereal solution, on evaporation, gave a red solid which, after crystallisation from benzene, had m. p. 240—255° (decomp.). This (2 g.) was not further investigated. The benzene liquors from which it crystallised gave, on standing, colourless crystals which, after several crystallisations from benzene, had m. p. 164·5—165·5°, and were identical with the lactone (IX?) obtained by Hewett (*loc. cit.*) by the action of concentrated sulphuric acid on γ-phenyl-γ-2-naphthylitaconic acid (Found : C, 80·2; H, 4·5. Calc. : C, 80·25; H, 4·5%). Boiling methyl-alcoholic hydrogen chloride transformed this lactone into the red methyl ester, m. p. 136°, of the acid (V) described in the following paragraph.

Addition of sodium chloride to the sodium carbonate extract referred to in the preceding paragraph precipitated the mixed sodium salts (24 g.) of the acids (V) and (VI). Two recrystallisations from water, followed by precipitation of the acid and crystallisation from benzene, gave pure 1-*keto*-3-*phenyl*-6 : 7-*benzindene*-2-*acetic acid* (V) (8·5 g.) in orange needles, m. p. 176—177° (Found : C, 80·2; H, 4·3. $C_{21}H_{14}O_3$ requires C, 80·25; H, 4·5%). The normal *methyl* ester, obtained by addition of excess of ethereal diazomethane to an ethereal solution of this acid, crystallised from methyl alcohol in red needles, m. p. 136° (Found : C, 80·4; H, 4·95; OMe, 9·25. $C_{22}H_{16}O_3$ requires C, 80·5; H, 4·9; OMe, 9·45%). The pseudo-*methyl* ester (VII), obtained from the acid by 20 minutes' boiling with methyl-alcoholic hydrogen chloride (10 c.c.), crystallised from methyl alcohol in bright red prisms, m. p. 83·5—84·5° (Found : C, 80·1; H, 5·25; OMe, 9·2%).

The aqueous mother-liquors from which the sodium salt of the acid (V) had crystallised were acidified, and the precipitated acid was converted into its potassium salt which, after two recrystallisations from water gave 1-*keto*-3-(2'-*naphthyl*)*indene*-2-*acetic acid* (VI). This crystallised from benzene–*cyclo*hexane in yellow prisms (6·5 g.), m. p. 150—153° (Found : C, 80·2; H, 4·3. $C_{21}H_{14}O_3$ requires C, 80·25; H, 4·5%). The normal *methyl* ester of (VI), prepared by treatment with ethereal diazomethane, formed yellow needles, m. p. 98—99° (from methyl alcohol) (Found : C, 80·45; H, 5·0; OMe, 9·4%). The pseudo-*methyl* ester (VIII), prepared from the acid (VI) by boiling methyl-alcoholic hydrogen chloride, crystallised from *cyclo*hexane in yellow needles, m. p. 101·5—102·5° (Found : C, 80·7; H, 5·0; OMe, 9·4%). This *pseudo*-ester depressed the m. p. of the normal ester to 93—94°. Both the normal and the *pseudo*-ester were hydrolysed by alcoholic potash to the acid from which they were obtained.

7-*Acetoxy*-1 : 2 : 5 : 6-*dibenzfluorenone* (X; R = COMe).—A solution of 1-keto-3-phenyl-6 : 7-benzindene-2-acetic acid (6 g.) in freshly distilled acetic anhydride (60 c.c.) was boiled for 15 minutes. The *acetate* (X; R = COMe) (6·2 g.) which crystallised on cooling was sufficiently pure for the next stage. For analysis, a specimen was crystallised twice from acetic acid and formed deep red needles, m. p. 245—246° (Found : C, 81·3; H, 4·3. $C_{23}H_{14}O_3$ requires C, 81·7; H, 4·1%). Hydrolysis of this acetate (2·5 g.) to 7-*hydroxy*-1 : 2 : 5 : 6-*dibenzfluorenone* (X; R = H) was effected by boiling for one minute with a solution of potassium hydroxide (1·8 g.) in methyl alcohol (90 c.c.). The resulting dark green solution was poured into much ice-water, the solution acidified, and the precipitated phenol collected and recrystallised from alcohol. Its dark purple solution gave black needles (2 g.), which decomposed above 250° (Found : C, 85·1; H, 4·3. $C_{21}H_{12}O_2$ requires C, 85·1; H, 4·05%). The *methyl ether* (X; R = Me), formed by the action of excess methyl sulphate on a solution of this phenol in alcoholic potassium hydroxide, crystallised from benzene in very dark red needles, m. p. 196—197° (Found : C, 85·1; H, 4·8; OMe, 9·5. $C_{22}H_{14}O_2$ requires C, 85·2; H, 4·5; OMe, 10·0%).

For conversion into 1 : 2 : 5 : 6-dibenzfluorene, the hydroxy-ketone (X; R = H) (0·5 g.) was intimately mixed with zinc dust (20 g.) and heated to dull redness in an atmosphere of hydrogen until sublimation ceased. The sublimate, dissolved in benzene–ligroin, was purified by chromatographic adsorption on alumina. The first fractions of the benzene eluate gave almost colourless needles of 1 : 2 : 5 : 6-dibenzfluorene, m. p. 170—173°, alone or mixed with an authentic specimen.

7-*Acetoxy*-1 : 2 : 5 : 6-*dibenz*-9-*fluorenol* was obtained when a solution of 7-acetoxy-1 : 2 : 5 : 6-dibenzfluorenone (0·1 g.) in acetic acid (10 c.c.) was boiled with zinc filings (0·1 g.) until the red colour had faded (about an hour). The precipitate formed by decanting the cooled solution into ice-water crystallised from alcohol in colourless needles, m. p. 222° (decomp.) (Found : C, 80·5; H, 4·9. $C_{23}H_{16}O_3$ requires C, 81·2; H, 4·7%). In another experiment, 7-acetoxy-1 : 2 : 5 : 6-dibenzfluorenone (2·5 g.) was reduced with zinc and acetic acid, and hydriodic acid (*d* 1·95; 8 c.c.) was added to the solution which had been decanted from the undissolved zinc. The mixture was then boiled for 2 hours, cooled, and poured into ice-cold sulphurous acid. The precipitate was collected, crystallised from benzene, then sublimed in a high vacuum at 170°, and finally recrystallised from benzene. The resulting colourless leaflets of 7-*hydroxy*-1 : 2 : 5 : 6-*dibenzfluorene* (XI; R = H) (1·8 g.) sublimed above 200°, but had no sharp m. p. (Found : C, 89·5; H, 4·95. $C_{21}H_{14}O$ requires C, 89·4; H, 5·0%). The *acetate* (XI; R = COMe), formed by the action of boiling acetic anhydride, crystallised from alcohol in colourless plates, m. p. 164—165° (Found : C, 85·0; H, 4·6. $C_{23}H_{16}O_2$ requires C, 85·2; H, 4·9%), and the *methyl ether* (XI; R = Me) was obtained by alternate treatment of a boiling solution of the phenol (100 mg.) in absolute alcohol (50 c.c.) with alcoholic potash and methyl sulphate (2·7 g. in all). This methylation was carried out in an atmosphere of hydrogen to avoid auto-oxidation. The methyl ether (XI; R = Me), which was not formed by the action of diazomethane on the phenol, formed colourless prisms (from benzene), m. p. 217—218° (Found : C, 89·5; H, 5·5. $C_{22}H_{16}O$ requires C, 89·2; H, 5·4%).

In an attempt to prepare 7-amino-1 : 2 : 5 : 6-dibenzfluorene, a mixture of 7-hydroxy-1 : 2 : 5 : 6-dibenzfluorene (0·2 g.), sodium bisulphite (0·9 g.), dioxan (1·1 c.c.), concentrated ammonia (2·2 c.c.), and water (2·2 c.c.) was heated in a sealed tube at 190—200° for 10 hours. The only pure material subsequently isolated was unchanged hydroxy-compound.

2-*Acetoxy*-3 : 4-(1' : 2'-*naphtha*)*fluorenone* (XII; R = COMe) was formed when a solution of the keto-acid (VI) (1·4 g.) in acetic anhydride (14 c.c.) was boiled for 30 minutes. The acetate which crystallised on cooling (1·45 g.) formed bright yellow needles (from toluene), m. p. 204—206° (Found : C, 81·7; H, 4·2. $C_{23}H_{14}O_3$ requires C, 81·7; H, 4·1%). Hydrolysis of this acetate (1 g.) with potassium hydroxide (0·5 g.) in methyl alcohol (25 c.c.) (3 minutes' boiling) gave a deep blue solution from which dilute acid precipitated 2-*hydroxy*-3 : 4-(1' : 2'-*naphtha*)*fluorenone* (XII; R = H). This crystallised from alcohol in claret-coloured needles, m. p. above 250° (decomp.) (Found : C, 85·15; H, 4·2. $C_{21}H_{12}O_2$ requires C, 85·1; H, 4·05%).

This hydroxy-ketone (0·5 g.) was distilled with zinc dust (30 g.) as described for the isomeride (X). The product crystallised from alcohol in greyish prisms, m. p. 189° [probably 3 : 4-(1' : 2'-naphtha)fluorene], but the amount was insufficient for analysis. The material from the mother-liquors was dissolved in acetone (5 c.c.) and boiled for 10 minutes with potassium methoxide (from 0·02 g. of potassium and 0·1 c.c. of methyl alcohol). After dilution with water the product was extracted with chloroform, and the material obtained from the extract was crystallised from alcohol. It had m. p. 155°.

1-Hydroxy-3-phenyl-6 : 7-benzindene-2-acetic acid was obtained when the keto-acid (V) (0·5 g.) was reduced in toluene solution (50 c.c.) by boiling for 1½ hours with 6N-hydrochloric acid (50 c.c.) and amalgamated zinc (2 g.). The acidic product was crystallised from aqueous acetic acid and then benzene–hexane, forming colourless prisms, m. p. 165—168°. The same product was obtained in better yield when a solution of the keto-acid (V) in acetic acid was boiled with zinc dust for 10 minutes and then with hydriodic acid for 2 hours. The pure hydroxy-acid crystallised from aqueous alcohol in colourless needles, m. p. 170° (Found : C, 80·3; H, 5·3. $C_{21}H_{16}O_3$ requires C, 79·75; H, 5·1%). The *methyl* ester, obtained with ethereal diazomethane, formed colourless prisms (from *cyclo*hexane), m. p. 105—106° (Found : C, 80·1; H, 5·8. $C_{22}H_{18}O_3$ requires C, 80·0; H, 5·45%). Failure to reduce the hydroxyl group is evidently due to steric hindrance.

3-(2′-Naphthyl)indene-2-acetic Acid.—A solution of the keto-acid (VI) (4 g.) in toluene (400 c.c.) was boiled for 4 hours with 6N-hydrochloric acid (400 c.c.) and amalgamated zinc (16 g.). Acidification of a sodium carbonate extract of the resulting toluene solution precipitated *3-(2′-naphthyl)indene-2-acetic acid*, which crystallised from benzene in colourless needles (1·5 g.), m. p. 177—178° (Found : C, 83·7; H, 5·4. $C_{21}H_{16}O_2$ requires C, 84·0; H, 5·3%).

Action of Fused Potassium Hydroxide on 1 : 2 : 5 : 6-Dibenzfluorenone.—The finely ground ketone (1 g.) was added to fused potassium hydroxide (2 g.) at 290°, and the temperature slowly raised to 340°. The cooled mass was extracted with water, and the solution acidified. Purification of the resulting acid gave 1 : 2′-dinaphthyl-2-carboxylic acid, m. p. 204° (from benzene) not depressed by admixture with an authentic specimen (Swain and Todd, *loc. cit.*). There was no evidence of the formation of 1 : 2′-dinaphthyl-1′-carboxylic acid.

4-Benzoyl-1-methoxynaphthalene (compare Fierz-David and Jaccard, *loc. cit.*).—Anhydrous aluminium chloride (40·5 g.) was slowly added to a stirred ice-cold solution of 1-methoxynaphthalene (24 g.) and benzoyl chloride (21·5 g.) in carbon disulphide (100 c.c.). The mixture was stirred at 0° for 6 hours, during which a deep red complex crystallised, and then decomposed with ice and hydrochloric acid. The carbon disulphide was removed in steam, the residue made alkaline, and passage of steam continued for 2 hours. The product, dried in ethereal solution, was distilled in a vacuum, and the distillate was recrystallised from alcohol, forming long colourless needles (24 g.), m. p. 80—81°.

3-Hydroxy-1 : 2-benzfluorenone.—A stirred mixture of 1-methoxy-4-benzoylnaphthalene (5 g.), anhydrous aluminium chloride (12 g.), and sodium chloride (4 g.) was heated in an oil-bath at 140° for 30 minutes. The cooled mass was decomposed with ice and hydrochloric acid, extracted with ether, and the ethereal extract shaken with dilute sodium hydroxide solution. Acidification of the alkaline solution precipitated crude 3-hydroxy-1 : 2-benzfluorenone (4·3 g.), a solution of which in acetic anhydride was boiled for an hour. On cooling, *3-acetoxy-1 : 2-benzfluorenone* (2·3 g.) crystallised. It formed dark yellow needles (from acetic acid), m. p. 184—185° (Found : C, 79·1; H, 4·5. $C_{19}H_{12}O_3$ requires C, 79·2; H, 4·2%). On hydrolysis this gave pure 3-hydroxy-1 : 2-benzfluorenone.

1 : 2-Benzfluorene.—A mixture of 3-hydroxy-1 : 2-benzfluorenone (2 g.) and zinc dust (20 g.) was heated in an atmosphere of hydrogen until distillation ceased. The distillate, in benzene solution, was purified by chromatographic adsorption on alumina, and gave 1 : 2-benzfluorene (chrysofluorene), m. p. 174—176°, not depressed by admixture with an authentic specimen, m. p. 182° (Cook *et al.*, J., 1934, 1727).

3-Acetoxy-1 : 2-benzfluorenol.—A solution of 3-acetoxy-1 : 2-benzfluorenone (2 g.) in acetic acid (200 c.c.) was boiled for 2 hours with zinc filings (6 g.). The colourless solution was decanted into ice water, and the precipitate was collected, dried, and crystallised several times from benzene–*cyclo*hexane. *3-Acetoxy-1 : 2-benzfluorenol* formed fine colourless needles, m. p. 157° (Found : C, 78·9; H, 4·9. $C_{19}H_{14}O_3$ requires C, 78·6; H, 4·8%). By further reduction with hydriodic acid in boiling acetic acid (2 hours) this was converted into *3-hydroxy-1 : 2-benzfluorene*, which, after sublimation at 175°/0·3 mm. and recrystallisation from benzene, formed colourless needles, m. p. 219° (Found : C, 87·8; H, 5·5. $C_{17}H_{12}O$ requires C, 87·9; H, 5·2%). Its *acetate* had m. p. 155—156° (Found : C, 83·1; H, 5·1. $C_{19}H_{14}O_2$ requires C, 83·2; H, 5·1%).

1-Methoxy-4-(2′-naphthoyl)naphthalene (XV).—Anhydrous aluminium chloride (38 g.) was slowly added to a stirred ice-cold solution of 2-naphthoyl chloride (32 g.) and 1-methoxynaphthalene (26 g.) in carbon disulphide (200 c.c.). The mixture was stirred at 0° for 6 hours, and worked up as described above for the benzoyl compound. The *ketone*, b. p. 250—260°/0·5 mm., crystallised from alcohol in pale yellow prisms, m. p. 114° (43 g.) (Found : C, 84·5; H, 5·2. $C_{22}H_{16}O_2$ requires C, 84·6; H, 5·1%).

3-Hydroxy-1 : 2 : 5 : 6-dibenzfluorenone (XVI).—A mixture of the foregoing ketone (10 g.), anhydrous aluminium chloride (10 g.), and sodium chloride (3 g.) was stirred for an hour while being heated in an oil-bath at 130—140°. The cooled melt was decomposed with ice and hydrochloric acid, and the insoluble material collected and extracted with a large volume of dilute sodium hydroxide solution. Acidification of the filtered solution precipitated crude 3-hydroxy-1 : 2 : 5 : 6-dibenzfluorenone. This was purified through its *acetate*, obtained by an hour's boiling with acetic anhydride. The acetate (5·6 g.), which crystallised from the solution on cooling, recrystallised from xylene in deep red needles, m. p. 262—265° (Found : C, 81·7; H, 4·0. $C_{23}H_{14}O_3$ requires C, 81·7; H, 4·1%). Hydrolysis of this acetate with boiling methyl-alcoholic potash solution was complete in 10 minutes. Dilution with water, filtration, and acidification of the filtrate precipitated *3-hydroxy-1 : 2 : 5 : 6-dibenzfluorenone* (XVI), which crystallised from anisole in dark brown needles which melted slowly above 300° (Found : C, 85·2; H, 4·05. $C_{21}H_{12}O_2$ requires C, 85·1; H, 4·05%).

3-Hydroxy-1 : 2 : 5 : 6-dibenzfluorene.—A solution of 3-acetoxy-1 : 2 : 5 : 6-dibenzfluorenone (2·5 g.) in acetic acid (600 c.c.) was boiled for 2 hours with zinc filings (10 g.) added in two portions. Decantation of the pale yellow solution into ice-water precipitated *3-acetoxy-1 : 2 : 5 : 6-dibenzfluorenol*, which crystallised from toluene in almost colourless needles, m. p. 237—238° (Found : C, 81·4; H, 4·8. $C_{23}H_{16}O_3$ requires C, 81·2; H, 4·7%). A solution of this carbinol in acetic acid (250 c.c.) and hydriodic acid (*d* 1·95; 10 c.c.) was boiled for 2 hours and poured into ice-cold sulphurous acid. The yellow precipitate (2·1 g.) was collected, dried, and recrystallised from benzene. For analysis, a specimen was sublimed at 195°/0·3 mm. and the sublimate was recrystallised from benzene. *3-Hydroxy-1 : 2 : 5 : 6-dibenzfluorene* formed colourless needles, m. p. 205—206° (decomp.) (Found : C, 89·6; H, 5·0. $C_{21}H_{14}O$ requires C, 89·4; H, 5·0%). Distillation of this phenol (0·5 g.) with zinc dust (20 g.) in a slow stream of hydrogen gave 1 : 2 : 5 : 6-dibenzfluorene (0·25 g.), m. p. 170°, alone or mixed with an authentic sample.

1 : 2 : 6 : 7-Dibenzfluorenol.—A solution of aluminium *iso*propoxide (4 g.) in *iso*propyl alcohol (30 c.c.) was added to a solution of 1 : 2 : 6 : 7-dibenzfluorenone (Martin, *loc. cit.*) (1 g.) in dry toluene (150 c.c.), and the mixture distilled slowly during 6 hours, the volume being kept constant by addition of *iso*propyl alcohol. More toluene was then added, and the cold solution treated with dilute sulphuric acid. Evaporation of the washed toluene solution gave 1 : 2 : 6 : 7-*dibenzfluorenol*, which crystallised from toluene in small colourless prisms (0·8 g.), m. p. 233—234° (Found : C, 89·2; H, 5·1. $C_{21}H_{14}O$ requires C, 89·4; H, 5·0%). When hydrogen bromide was passed into a warm suspension of this carbinol (0·1 g.) in acetic acid (15 c.c.) it dissolved, and *9-bromo-1 : 2 : 6 : 7-dibenzfluorene* crystallised. It formed long, pale yellow needles (from *cyclo*hexane) which decomposed at 186—187°, after darkening (Found : Br, 22·9. $C_{21}H_{13}Br$ requires Br, 23·2%).

1 : 2 : 6 : 7-Dibenzfluorene (XVII).—1 : 2 : 6 : 7-Dibenzfluorenone (0·2 g.) was heated in a sealed tube for 6 hours with 50% hydrazine hydrate. The hydrocarbon was isolated from the products by vacuum sublimation followed by recrystallisation from benzene. 1 : 2 : 6 : 7-*Dibenzfluorene* formed colourless plates, m. p. 294—295° (Found : C, 94·5;

H, 5·6. $C_{21}H_{14}$ requires C, 94·7; H, 5·3%). The yields, using 0·6, 1·5, and 2 c.c. of 50% hydrazine hydrate were 0·17, 0·08, and 0·06 g., respectively. The other products consisted of red material, probably partly the *azine*, which did not sublime (Found, after recrystallisation: C, 90·4; H, 4·4. $C_{42}H_{24}N_2$ requires C, 90·65; H, 4·3%).

Reduction of 2 : 3 : 6 : 7-*Dibenzfluorenone* (compare Martin, *loc. cit.*).—A mixture of 2 : 3 : 6 : 7-dibenzfluorenone (3 g.) and 50% hydrazine hydrate (18 c.c.) was heated in a sealed tube at 210° for 8 hours. The product was sublimed at 210—220°/0·2 mm., and the sublimate, after recrystallisation from benzene, gave 2 : 3 : 6 : 7-dibenzfluorene (1·1 g.), m. p. 281—282°.

The residue from the sublimation was extracted with hot benzene. The filtered extract gave, on cooling, colourless needles (0·13 g.), probably consisting of 2 : 3 : 6 : 7 : 2′ : 3′ : 6′ : 7′-*tetrabenz*-9 : 9′-*difluorenyl* (XIX). This had m. p. 310° (decomp.) (from xylene) (Found: C, 95·0; H, 5·3. $C_{42}H_{26}$ requires C, 95·1; H, 4·9%). The residue insoluble in benzene crystallised from nitrobenzene in dark red needles, not molten at 310°, probably consisting of 2 : 3 : 6 : 7 : 2′ : 3′ : 6′ : 7′-*tetrabenzbisfluorenylideneazine* (XX) (Found: C, 90·7; H, 4·1; N, 5·2. $C_{42}H_{24}N_2$ requires C, 90·65; H, 4·3; N, 5·0%).

Chloromethylation of 9 : 10-*Dihydrophenanthrene*.—The dihydrophenanthrene was obtained from purified phenanthrene by hydrogenation over copper chromite at 150° and 115 atm. (compare Fieser and Johnson, *J. Amer. Chem. Soc.*, 1939, **61**, 169).* Paraformaldehyde (3·6 g.) was added to an ice-cold solution of 9 : 10-dihydrophenanthrene (10 g.) in acetic acid (30 c.c.), and dry hydrogen chloride was passed into the suspension until the paraformaldehyde had dissolved. The most satisfactory results were obtained when this mixture was kept at room temperature for 10 days. The whole was then poured into water, extracted with benzene, and the benzene extract was washed, dried, and distilled. Unchanged dihydrophenanthrene (3·75 g.) distilled at 130—140°/0·5 mm. The fraction, b. p. 140—180°/0·5 mm. (5 g.), seemed to consist largely of chloromethyl compound. A solution of this fraction (0·65 g.) and anhydrous sodium acetate (0·65 g.) in acetic acid (5 c.c.) was boiled for an hour. The product was hydrolysed with methyl-alcoholic potash and gave 3-hydroxymethyl-9 : 10-dihydrophenanthrene (0·2 g.), which crystallised from ether–ligroin in colourless needles, m. p. 89—92°.

A solution of the crude chloromethyl compound (2 g.) in alcohol (25 c.c.) and water (5 c.c.) was boiled with zinc dust (3 g.) for 3 hours. The product, distilled from an air-bath at 130°/0·4 mm., was free from halogen and was heated with palladium-black (0·1 g.) at 280° for 13 hours. This product of dehydrogenation was distilled at 140°/0·3 mm., the distillate (1·2 g.) crystallising. It gave a picrate, m. p. 137°, from which was obtained a hydrocarbon, m. p. 61—62° (3-methylphenanthrene and its picrate have m. p. 62—63° and 137°, respectively).

Condensation of 9 : 10-*Dihydrophenanthrene with Benzoyl Chloride*.—A solution of benzoyl chloride (4·85 g.) in nitrobenzene (10 c.c.) was added dropwise, during ½ hour, to an ice-cold solution of anhydrous aluminium chloride (14·6 g.) and 9 : 10-dihydrophenanthrene (10 g.) in nitrobenzene (100 c.c.). The mixture was kept at 0° for a further 2 hours, and then at room temperature for 20 hours. After decomposition with ice and hydrochloric acid, the nitrobenzene was removed in steam, and the residual ketone was extracted with ether. Distillation gave an oil (8·5 g.), b. p. 228—233°/0·5 mm., which did not crystallise. It gave a homogeneous 2 : 4-*dinitrophenylhydrazone*, which crystallised from ethyl acetate in deep salmon-coloured needles, m. p. 234—235° (Found: C, 69·9; H, 4·4. $C_{27}H_{20}O_4N_4$ requires C, 69·8; H, 4·3%). The *oxime*, prepared by treatment of the distilled ketone with hydroxylamine hydrochloride in pyridine at 100°, formed colourless needles, m. p. 219° (from alcohol) (Found: C, 83·7; H, 6·1. $C_{21}H_{17}ON$ requires C, 84·3; H, 5·7%).

For oxidation, a solution of this liquid ketone (1·3 g.) in acetic acid (10 c.c.) was boiled for a few minutes with a solution of chromic acid (1·2 g.) in water (2 c.c.). The resulting quinone (0·35 g.) crystallised from chlorobenzene in orange needles, m. p. 217°, raised to 219° by vacuum sublimation, with two further crystallisations. This m. p. is in agreement with that given by Bachmann (*J. Amer. Chem. Soc.*, 1935, **57**, 555) for 2-benzoylphenanthraquinone (m. p. 218°).

Confirmation that the original ketone was essentially 2-benzoyl-9 : 10-dihydrophenanthrene was obtained as follows. 9 : 10-Dihydro-2-phenanthroic acid (Burger and Mosettig, *ibid.*, p. 2731; 1936, **58**, 1857) (1·4 g.) was converted into its chloride by 2 hours' boiling with thionyl chloride (12 c.c.). The solid obtained by removal of the excess of thionyl chloride under reduced pressure was dissolved in benzene (30 c.c.), and the solution was added to a cold suspension of anhydrous aluminium chloride (0·9 g.) in benzene (9 c.c.). The mixture was boiled for 2 hours, and the product isolated in the usual way. The distilled ketone (0·9 g.) solidified when triturated with alcohol. After recrystallisation from alcohol, 2-*benzoyl*-9 : 10-*dihydrophenanthrene* (XXI) formed colourless needles, m. p. 72—73° (Found: C, 88·9; H, 5·6. $C_{21}H_{16}O$ requires C, 88·7; H, 5·6%). Its 2 : 4-dinitrophenylhydrazone, m. p. 235°, was identical with that obtained from the oily ketone prepared from 9 : 10-dihydrophenanthrene and benzoyl chloride.

2-*Phenylacetylfluorene* (XXII).—Anhydrous aluminium chloride (42 g.) was added to an ice-cooled solution of fluorene (26 g.) and phenylacetyl chloride (25 g.) in carbon disulphide (100 c.c.). The mixture was stirred at 0° for 6 hours, decomposed with ice and hydrochloric acid, and the carbon disulphide and excess of fluorene removed in steam. Crystallisation of the residue from benzene gave 2-phenylacetylfluorene (28 g.), m. p. 153° (compare Pāpcke, *Ber.*, 1888, **21**, 1331). An equally good result was obtained when the condensation was carried out in nitrobenzene solution at room temperature (20 hours).

When this ketone was heated at 350° for 3 hours about 60% was recovered. The mother-liquors, after vacuum distillation, gave a very small amount of colourless needles (from toluene), m. p. 265—270°. This was not investigated.

Reduction of 2-*Phenylacetylfluorene*.—(*a*) Clemmensen reduction, using the modification of Martin (*J. Amer. Chem. Soc.*, 1936, **58**, 1438) gave, in 45% yield, a *compound* which crystallised from toluene in colourless prisms, m. p. 273—274°. This probably consisted essentially of a pinacol (Found: C, 88·95; H, 5·9. $C_{42}H_{34}O_2$ requires C, 88·4; H, 6·0%). (*b*) By using anisole instead of toluene as the inert solvent in the above reduction, and by increasing the duration of boiling to 72 hours, there was obtained, in 25% yield, a *hydrocarbon* which crystallised from alcohol in long colourless needles, m. p. 146° (Found: C, 93·3; H, 6·8; *M*, Rast, 234. $C_{21}H_{18}$ requires C, 93·3; H, 6·7%; *M*, 270). (*c*) When a mixture of 2-phenylacetylfluorene (1 g.) and 50% hydrazine hydrate (5 c.c.) was heated in a sealed tube at 270° for 7 hours the *azine* was the chief product. This formed yellow needles (from anisole), m. p. 285—288°. Satisfactory analytical figures were not obtained, probably owing to retention of solvent (Found: C, 87·5; H, 5·8. $C_{42}H_{32}N_2$ requires C, 89·4; H, 5·7%). A mixture of this azine (0·5 g.) and sodium ethoxide solution (from 0·5 g. of sodium and 7 c.c. of alcohol) was heated in a sealed tube at 200° for 8 hours. The product was extracted with ether, distilled in a vacuum, and the distillate recrystallised from methyl alcohol, forming yellow prisms, m. p. 113—114°. This *hydrocarbon* should be 2-(β-phenylethyl)fluorene (Found: C, 93·5; H, 6·7; *M*, Rast, 236. $C_{21}H_{18}$ requires C, 93·3; H, 6·7%; *M*, 270). (*d*) An impure specimen of the foregoing hydrocarbon, m. p. 113°, was obtained from the semicarbazone, m. p. 221—224°, of 2-phenylacetylfluorene, by 8 hours' heating at 190—200° with alcoholic sodium ethoxide.

cis-*Indane*-1 : 2-*dicarboxylic Anhydride* (XXIII).—Ethyl indene-2 : 3-dicarboxylate was prepared by the method of Bougault (*Compt. rend.*, 1914, **159**, 745). A solution of this ester (2 g.) in alcohol (50 c.c.) was shaken with hydrogen

* This hydrogenation was carried out in an autoclave purchased from a grant from the Carnegie Trust for the Universities of Scotland.

and palladium-black (0·1 g.) until absorption ceased. The saturated ester was not obtained crystalline and was hydrolysed by boiling alcoholic potash to *cis*-indane-1 : 2-dicarboxylic acid, m. p. 228° (1·4 g.). In all, 20·5 g. of this acid were obtained from 30 g. of the unsaturated ester. A suspension of the saturated acid (6·7 g.) in acetyl chloride (30 c.c.) was boiled for 6 hours. The solvents were removed, and the residue distilled from an air-bath at 145°/0·2 mm. The distillate (3·5 g.) crystallised on standing, and recrystallised from benzene–*cyclo*hexane in colourless plates of cis-*indane*-1 : 2-*dicarboxylic anhydride*, m. p. 97—98° (Found : C, 70·4; H, 4·1. $C_{11}H_8O_3$ requires C, 70·2; H, 4·3%). This anhydride, which must be derived from the *cis*-acid, is hydrolysed to the acid, m. p. 228°, from which it was prepared. The latter therefore has the *cis*-configuration. The anhydride reacts with alcohol to give the *monoethyl* ester, m. p. 123—124° (Found : C, 67·1; H, 6·2. $C_{13}H_{14}O_4$ requires C, 66·7; H, 6·0%).

We are much indebted to Imperial Chemical Industries Ltd. (Dyestuffs Division) for financial provision which has enabled one of us (R. W. G. P.) to carry out the experiments here recorded, and also for gifts of chemicals. All analyses were micro-analyses carried out by Mr. J. M. L. Cameron.

UNIVERSITY OF GLASGOW. [*Received, June 26th*, 1944.]

NOTE.

The Preparation of 1 : 2 : 3-*Trinitronaphthalene.* By HERBERT H. HODGSON and DAVID E. HATHWAY.

THE ease with which toluene-*p*-sulphon-1-naphthalide is dinitrated in the 2- and the 4-position (Hodgson and Walker, J., 1934, 180) has been utilised for the preparation of 2 : 3 : 4-*trinitrotoluene*-p-*sulphon*-1-*naphthalide* from 3-nitrotoluene-*p*-sulphon-1-naphthalide (Hodgson and Hathway, this vol., p. 21). Homonuclear dinitration was established by oxidation of the above compound to phthalic acid with neutral aqueous potassium permanganate. Subsequent hydrolysis by concentrated sulphuric acid to 2 : 3 : 4-*trinitro*-1-*naphthylamine* (cf. Hodgson and Birtwell, J., 1943, 433), diazotisation by Hodgson and Walker's procedure (J., 1933, 1620), and decomposition by cuprous oxide in ethyl alcohol (Hodgson and Turner, J., 1942, 748) afforded 1 : 2 : 3-*trinitronaphthalene*.

Dinitration of 3-*Nitrotoluene*-p-*sulphon*-1-*naphthalide*.—Nitric acid (3 c.c., *d* 1·42) in which a crystal of sodium nitrite had been dissolved, was added with vigorous stirring at 50° to a finely divided suspension of 3-nitrotoluene-*p*-sulphon-1-naphthalide (6 g.) in glacial acetic acid (12 c.c.), and the mixture heated to 75°; dinitration then occurred, the temperature rising to 100°. On cooling, 2 : 3 : 4-*trinitrotoluene*-p-*sulphon*-1-*naphthalide* (4 g.) slowly crystallised in fine, cream, felted needles, which were filtered off, washed successively with glacial acetic acid, methyl alcohol, and ligroin, and finally dissolved in hot glacial acetic acid, from which it crystallised on cooling in buff-coloured rods, m. p. 190° (Found : N, 12·95. $C_{17}H_{12}O_8N_4S$ requires N, 12·96%).

Orientation of the Nitro-groups. The trinitro-compound (1·2 g.) was boiled for 5 hours with a solution of potassium permanganate (3·5 g.) in water (50 c.c.). Sulphur dioxide was then passed through the chilled acidified solution to dissolve the manganese oxides, and the mixture was heated, filtered from insoluble organic material, and the filtrate evaporated to dryness; the residue of crude phthalic acid was purified by dissolution in ether, removal of the ether from the extract, and crystallisation of the residual phthalic acid from hot water; m. p. and mixed m. p. 195°.

2 : 3 : 4-*Trinitro*-1-*naphthylamine* was formed when a cold solution of the naphthalide (1 g.) in sulphuric acid (5 c.c., *d* 1·84) was heated at 30° for 15 minutes, the mixture poured on ice, triturated with aqueous ammonia, and the free amine (0·7 g.) removed; it crystallised from ethyl alcohol–acetone (1 : 2) in orange-yellow, micro-crystals, m. p. 220° (Found : N, 20·3. $C_{10}H_6O_6N_4$ requires N, 20·2%).

1 : 2 : 3-*Trinitronaphthalene*.—The trinitro-naphthalide (1·3 g.) was stirred into sulphuric acid (7 c.c., *d* 1·84) below 10°, a solution of sodium nitrite (0·3 g.) in sulphuric acid (2 c.c., *d* 1·84) added, and the mixture stirred into glacial acetic acid (25 c.c.) below 20°. Stirring was continued for 30 minutes, after which the diazotised solution was stirred into a suspension of red cuprous oxide (0·8 g.) in ethyl alcohol (50 c.c.). After the reaction had subsided, the mixture was poured on ice (300 g.), filtered, the filtrate steam-distilled to remove volatile compounds, and the flask liquor extracted with ethylene dichloride (100 c.c.) to remove the 1 : 2 : 3-trinitronaphthalene, the extract being washed with aqueous sodium carbonate followed by water. On partial removal of the ethylene dichloride from the dried extract, the 1 : 2 : 3-*trinitronaphthalene* (0·3 g.) was deposited; it recrystallised from chloroform in pale orange parallelepipeds, m. p. 190° (Found : N, 16·0. $C_{10}H_5O_6N_3$ requires N, 16·0%). This compound can be sublimed, and also gives a blood-red colour with aqueous acetone containing sodium hydroxide, but no pronounced coloration with alcoholic potassium hydroxide.

The authors thank Imperial Chemical Industries Limited, Dyestuffs Division, for gifts of chemicals.—TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, August 24th*, 1944.]

OBITUARY NOTICES.

HORACE EDWARD BROTHERS.

1863—1944.

HORACE EDWARD BROTHERS died at his home at Old Colwyn on July 3rd, 1944, in his 81st year.

He was a son of the late Alfred Brothers of Manchester, a pioneer of astronomical photography, whose photographs of the solar eclipse at Syracuse in 1870 showed that the corona is an appendage of the sun.

Brothers received his early education at Alderley Edge, and at Chorlton High School, Manchester. From 1881 to 1885, he attended Owens College, studying chemistry under Roscoe and Schorlemmer, and physics under Balfour Stewart. He took a new course of studies specially designed to qualify for a technical position in industry at a time when the employment of scientifically trained men by manufacturers was rare. From 1885 to 1899 he was analyst and technical manager of a chemical works in the Potteries, engaged in the extraction of cobalt and nickel and their compounds, and in the manufacture of borax and boric acid.

In 1899 he became one of H.M. Inspectors of Factories, and in 1903 was deputed to investigate chemically the means of ventilation, and effects of artificial illumination in workrooms in the flax and jute works in Scotland. He also took part in a special enquiry into the dangers peculiar to chemical industry, and the most effective means for prevention of accidents to workers in these factories. The enquiry led to the drawing up of a code of " Regulations for Chemical Works " issued by the Home Office Factory Department in 1922. These Regulations still prove effective, and many of their requirements have been embodied in the new Factory Act of 1938.

Brothers retired from the Civil Service in 1925. He was a Fellow of the Royal Institute of Chemistry, a Fellow of the Chemical Society for nearly 60 years, and a life Member of the Society of Chemical Industry. He was a joint author of a paper on phenolic constituents of blast furnace tars published in the *Journal* in 1886.

(MISS) D. M. BROTHERS.

DAVID GWYNNE DAVIES.

1907—1944.

DAVID GWYNNE DAVIES died in tragic circumstances at Malvern on April 16th, 1944. He was the only son of Mr. J. R. Davies, sometime Headmaster of Dowlais Boys' School, Merthyr Tydvil, and was educated at his father's school and at Merthyr Tydvil Intermediate School. In 1925 he entered the University College of Wales, Aberystwyth, as a student in the Teacher's Training Department and graduated B.Sc. in 1928 with Second Class Honours in Chemistry. After completing the Diploma in Education, he pursued a course of research under the direction of Mr. C. R. Bury and was awarded the Ph.D. degree in 1931. Their work is published as a series of papers in the *Journal*.

Subsequently Davies was appointed Assistant-Lecturer in the Department of Chemistry at his College, where he proved to be a very capable teacher and research worker. Becoming interested in the study and teaching of micro-analytical methods, he assisted in the foundation of the Microchemical Club. In 1934 he became an officer in the College contingent of the Officers' Training Corps and in 1936 succeeded to the command. At the outbreak of war he organised and commanded the University of Wales (No. 2) Reception Unit at Cardiff and subsequently served with a training unit of the South Wales Borderers. He returned to Aberystwyth in 1940 to command the Senior Training Corps, in which he attained the rank of Major, and to resume his teaching work in the department of Chemistry. In carrying out these duties in the service of the associated University Colleges of London and Wales with efficiency and tact, he earned the commendation and gratitude of both institutions

T. CAMPBELL JAMES.

GEORGE STALLARD.

1854—1944.

GEORGE STALLARD, who died on April 5th, 1944, was one of the oldest Fellows of the Chemical Society, having been elected in December, 1879. He was the *doyen* of Science Masters in public schools, having held appointments at St. Paul's and Rugby, where he organised the teaching of chemistry on modern lines with strong emphasis on laboratory work.

He was born on July 6th, 1854, the son of Mr. George Stallard of Havant, the owner of a parchment factory. He was educated at Hurstpierpoint College and proceeded with a scholarship to Keble College, Oxford, whence in 1876 he took an Honours Degree (first class) in Natural Science, with chemistry as his principal subject.

As there was no chemical teaching at Keble College, Stallard went for lectures and laboratory work to the University Chemical Department at the Museum. Odling was then the Professor, and W. W. Fisher and

John Watts superintended the laboratory work. Stallard found Watts a well-informed and painstaking teacher and was fortunate in securing him as his private tutor. Stallard always acknowledged his great indebtedness to Watts.

After taking his degree, Stallard was appointed Science Master at the Bedford County School at Elstow, which had adopted a modern curriculum but where Stallard had to teach several subjects besides chemistry. From there in 1878 he went to St. Paul's, then in the City, as its first Science Master, although still having also to teach other subjects than chemistry. F. W. Walker was Headmaster and was not credited with much enthusiasm for science teaching. He began by giving Stallard the option of teaching some other subject than chemistry. Stallard preferred to adhere to chemical teaching and Walker, evidently impressed by his sincerity, afterwards gave him every encouragement, so that Stallard looked back on his five years at St. Paul's as the happiest time in his school life.

His first pupil was a new boy who desired to take up chemistry and who had not been changed by Walker's advocacy of other subjects. He came with the boy to Stallard's room and said, " I hand over this boy to your care, body and soul." That boy was my brother, the late Professor M. J. R. Dunstan, who from St. Paul's gained a Postmastership at Merton College, Oxford, took an Honours Degree in Chemistry, and became successively Principal of the Wye Agricultural College and the Cirencester Agricultural College.

On going to Rugby in 1883, Stallard found Jex-Blake as Headmaster and again in addition to chemistry was required to teach other subjects. There was then no proper laboratory. In 1887, Percival succeeded Jex-Blake. He came from Clifton, where Tilden had made great headway in the teaching of chemistry. Stallard was now able to devote himself entirely to chemistry and, although there was no adequate laboratory until 1905, he continued to make chemistry of increasing interest to the boys, with whom he had some conspicuous successes. Among these were Nevil Sidgwick, now Professor at Oxford, and Sir Will Spens, Vice-Chancellor and Master of Corpus Christi College, Cambridge.

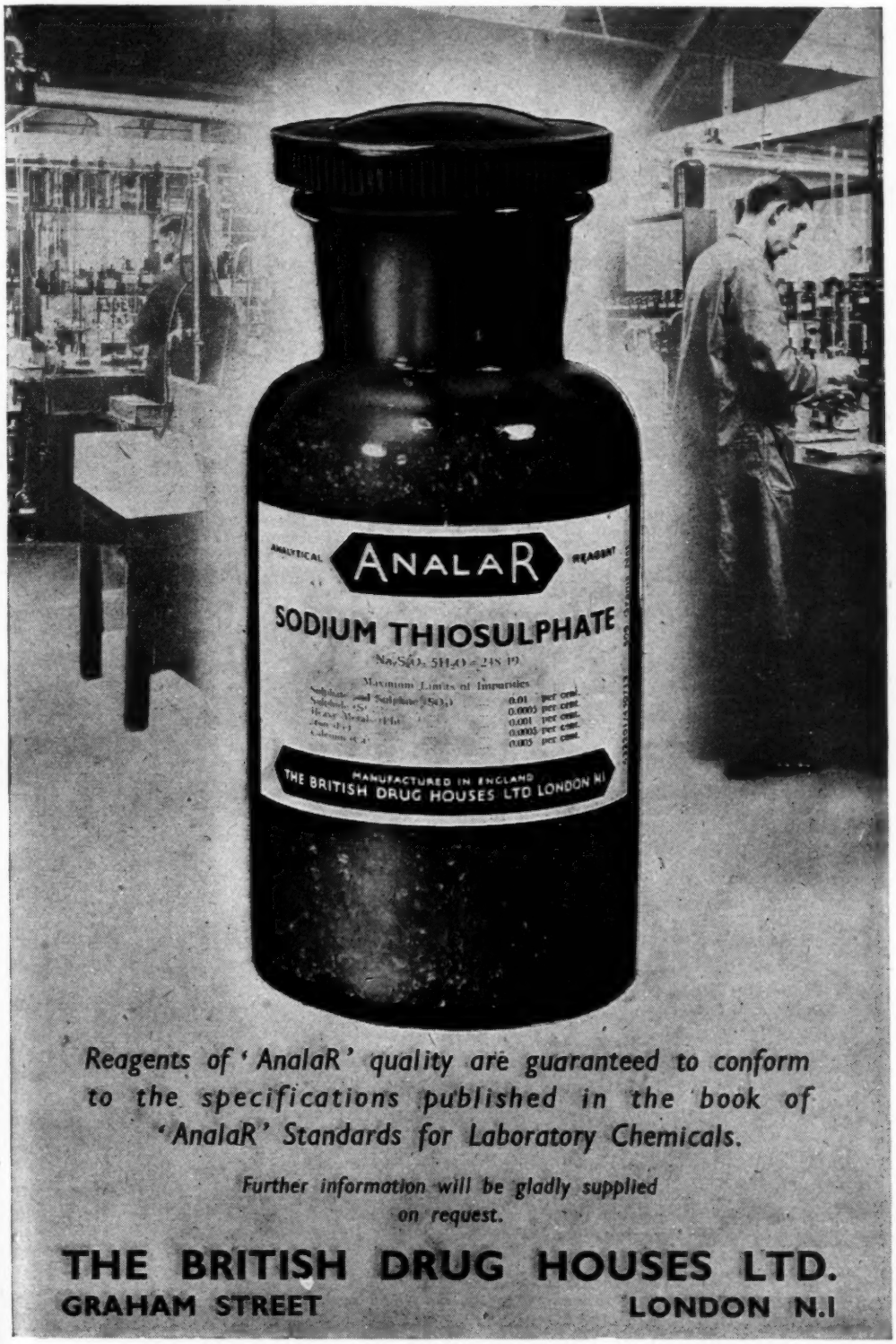
Stallard soon acquired great influence in the school. In 1893 he became a House Master, built Tudor House, and firmly established chemistry in the school curriculum, largely owing to the improvements he made in laboratory teaching. He took immense trouble in teaching both the ordinary boys and those whom he was preparing for scholarship examinations. He retired in 1913.

In 1887, the British Association appointed a Committee to report on the teaching of chemistry in schools, of which Dr. W. J. Russell was chairman and I was secretary. Stallard was one of the members and with Francis Jones (Manchester), Dunn (Bath), and Shenstone (Clifton), took an active part in the proceedings.

Above all Stallard was a schoolmaster but with many other interests. He was interested in art, was well read in English literature, was a good linguist, was active in sport, and while at Rugby was often to be seen in the hunting field and at the rifle range. He was also a keen mountaineer, and spent several vacations climbing in the Dauphiné, where later he built a Chalet. Here he hunted chamois and in Sardinia moufflon.

He died within a short time of his wife, his devoted companion, who will also be remembered as the good friend of many generations of schoolboys.

WYNDHAM R. DUNSTAN.



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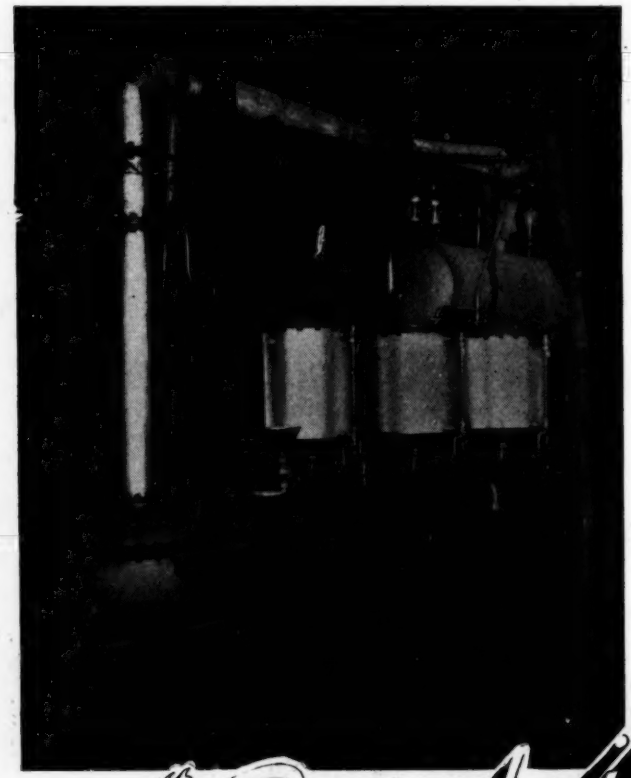

"Staybrite"

Solvent Extraction and Rectification Plant in "Staybrite" Steel constructed by Aluminium Plant and Vessel Co., Ltd., London, S.W.18

FIRTH-VICKERS STAINLESS STEELS LTD SHEFFIELD

PRINTED IN GREAT BRITAIN BY RICHARD CLAY AND COMPANY, LTD., BUNGAY, SUFFOLK.